Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Revisiting liquorice (*Glycyrrhiza glabra* L.) as anti-inflammatory, antivirals and immunomodulators: Potential pharmacological applications with mechanistic insight.

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A R T I C L E I N F O

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A B S T R A C T

Background: *Glycyrrhiza glabra* L. (*G. glabra*) commonly known as liquorice is one of the highly exploited and utilized medicinal plant of the world. Since ancient times liquorice is considered as an auspicious and valuable traditional medicine across the world for treatment of various ailments.
Method: Several electronic online scientific databases such as Science Direct, PubMed, Scopus, Scifinder, Google Scholar, online books and reports were assessed for collecting information. All the collected information was classified into different sections to meet the objective of the paper.
Results: The electronic database search yielded 3908 articles from different countries. Out of them one ninety-eight articles published between 1956 and 2021 were included, corresponding to all detailed review on *G. glabra* and research on anti-inflammatories, antivirals and immunomodulatory through pre-clinical and clinical models. From all selective area of studies on *G. glabra* and its bioactive components it was established (including molecular mechanisms) as a suitable remedy as per the current requirement of pandemic situation arise through respiratory tract infection.
Conclusion: Different relevant studies have been thoroughly reviewed to gain an insight on utility of liquorice and its bioactive constituents for anti-inflammatories, antivirals and immunomodulatory effects with special emphasized for prevention and treatment of COVID-19 infection with possible mechanism of action at molecular level. Proposed directions for future research are also outlined to encourage researchers to find out various mechanistic targets and useful value added products of liquorice in future investigations.

List of Abbreviation

AIM (Absent in melanoma);
ASC (Apoptosis-associated speck-like protein cell);
BMDMs (Bone marrow-derived macrophages);
BMI (Body mass index);
CD4+ (Cluster of differentiation);
COX (Cyclooxygenase),
CPE (Cytopathic effect);
CXCL (Chemokine (C-X-C motif) ligand 2);
DHV (Duck Hepatitis Virus);
ERK1/2 (Extracellular signal-regulated kinases);
Fox O (Forkhead box O);
H1N1 (Hemagglutinin Type 1 and Neuraminidase Type 1);
HIF-1 (Hypoxia-inducible factor);
10-HDoHE (Hydroxydocosahexaenoic acid);
5-HETE (5-Hydroxyeicosatetraenoic acid);
HMGP B1 (High mobility group protein B1);
ICAM-1 (Intercellular adhesion molecule-1);
IFN-γ (Interferon-gamma);

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IL	(Interleukin);
iNOS	(Inducible nitric oxide synthase);
IgE:	(Immunoglobulin E);
JNK	(c-Jun N-terminal kinases);
LOX	(Lysyl oxidase);
LPS	(Lipopolysaccharide);
LTB4	(Leukotriene B4);
MAPK	(Mitogen-activated protein kinase);
MDC	(Monocyte-derived chemokine);
MHC	(Major histocompatibility complex);
Mpro	(Main protease);
mRNA	(Messenger RNA);
NF-κB	(Nuclear factor kappa-light-chain-enhancer of activated B cells);
NLR	(Nucleotide-binding domain leucine-rich repeat);
NO	(Nitric oxide);
NOD	(Nucleotide-binding oligomerization domain-like receptors);
OVA	(Ovalbumin);
PBMC	(Peripheral blood mononuclear cell);
PDEP5	(Phosphodiesterase-5);

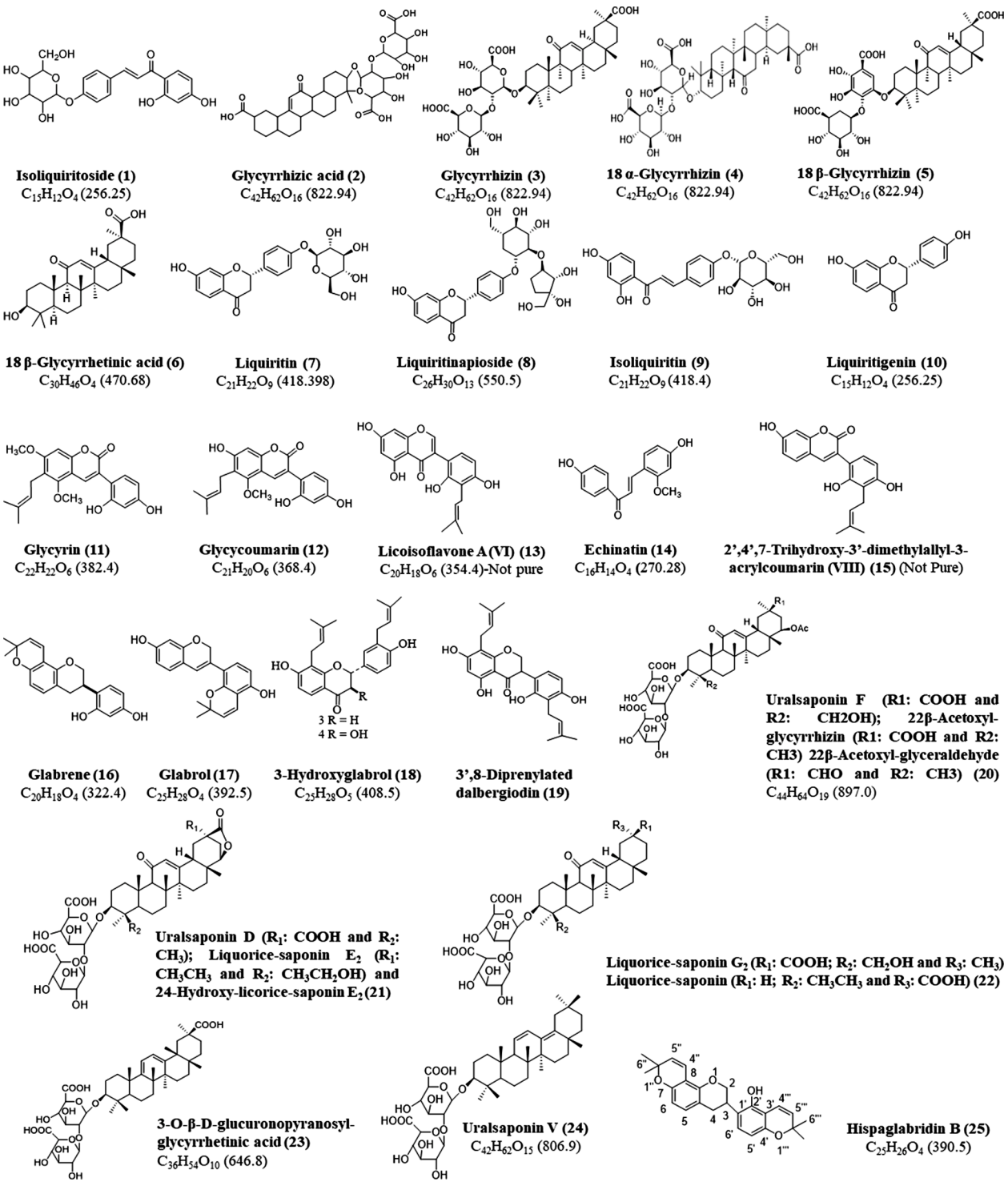

Fig. 1. Chemical structure of phytochemicals present in *G. glabra* L.

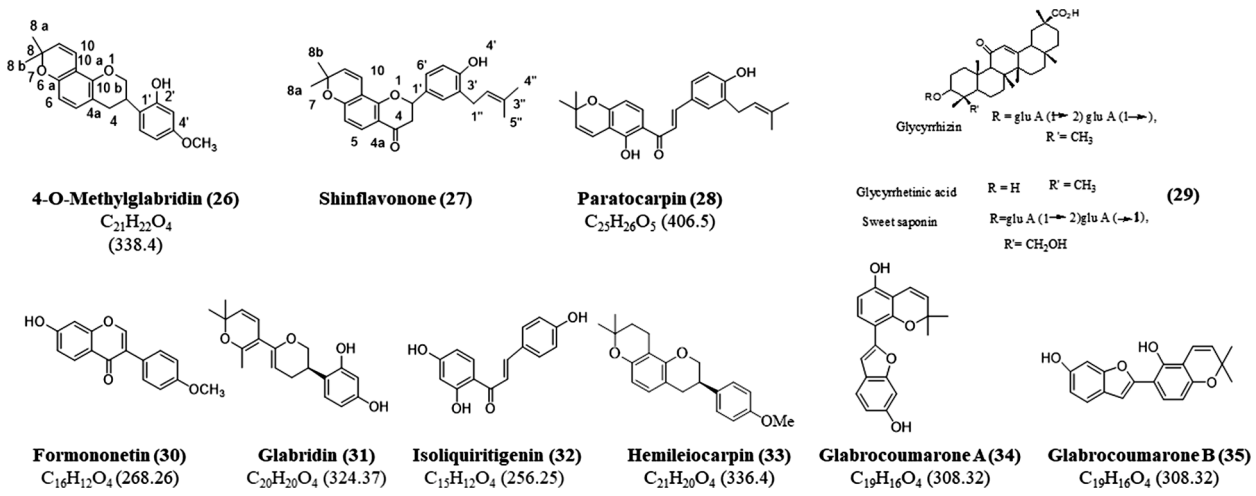

Fig. 1. (*continued*).

PDL-1 (Programmed death-ligand-1);
PGE2 (Prostaglandin E2);
PI3K-Akt (Phosphatidylinositol-3-kinase);
RANTES (Regulated upon Activation, Normal T Cell Expressed and Presumably Secreted);
ROS (Reactive oxygen species);
sGC/cGMP- PKG (Soluble guanylyl cyclase dependent protein kinase);
sMAD (Mothers against decapentaplegic homolog);
STAT (Signal transducer and activator of transcription);
STIM (Stromal interaction molecule);
TARC (Thymus- and activation-regulated chemokine);
TGF (Transforming growth factor);
Th (T helper cell);
TLR-9 (Toll-like receptor 9);
TNF-α (Tumor necrosis factor-α);
TRPC (Transient receptor potential canonical);
TRPV (Transient receptor potential cation channel subfamily V member);
TXB2 (Thromboxane B2) and
VEGF (Vascular endothelial growth factor).

Introduction

Glycyrrhiza glabra L. (Fabaceae) (common name liquorice) is a valuable medicinal plant. Its name derives from the Greek words 'glykos' that means sweet and 'rhiza' that means root (Sharma et al., 2018). The genus Glycyrrhiza comprises more than 30 species that are extensively dispersed worldwide mainly at Mediterranean regions of Asia (Sharifi-Rad et al., 2021). This plant has been documented and reviewed as traditional remedy for the prevention of painful swellings, cough, colds, and influenza. (Pastorino et al., 2018; Hosseini et al., 2020; Nasiri et al., 2020). *G. glabra* and its bioactive phytochemicals holds multiple pharmacological activities like, antidemulcent, expectorant, antiulcer, anti-inflammatory, anticancer and antidiabetic as an evidence from various review held in recent past (Pandey et al., 2017; Sharma et al., 2018). Wider utility in traditional medicinal system and proven scientific validated studies makes liquorice and its bioactive compounds (Fig. 1) as drug of choice to explore it more precisely for multiple health benefit possibilities as an evidence from many published studies reviewed in past (Revers, 1956; Ren and Wang, 1988; Olukoga and Donaldson, 2000; Saxena, 2005; Asl and Hosseinzadeh, 2008; Kaur et al., 2013; Kao et al., 2014; Hosseinzadeh and Nassiri-Asl, 2015; Yang et al., 2015; Dastagir and Rizvi, 2016; Pastorino et al., 2018; Sharma et al., 2018; Bredin, 2019; Mamedov and Egamberdieva, 2019; Batiha et al., 2020; Chen et al., 2020a; Jiang et al., 2020; Kwon et al., 2020; Rehman et al., 2020; Wang et al., 2020; Hasan et al., 2021; Sharifi-Rad et al., 2021). Further, utility through novel drug delivery specially nanomedicine approaches, cosmeceutical application and as an animal feed alternative are well discussed and reviewed recently (Alagawany et al., 2019; Ciganovic et al., 2019; Rani et al., 2021). The current piece of this illustrative work will provide motivation on growing interest in coming years about concept of drug repurposing for a better understanding of the indication based drug discovery strategies for the treatment of many related clinical and pathological conditions and thus may direct future research.

In nutshell, the present review documented recent scientific evidence available on pharmacology focussing antiinflammatory, antivirals and immunomodulatory effect with special emphasized for the prevention and treatment of COVID-19 infection by involvement of molecular mechanism to direct future research for bringing liquorice to develop several value added products for commercialization.

Materials and methods

The exhaustive search of literature was accomplished with the information retrieved by using online electronic search engines/databases/publishers and websites such ACS, Google Scholar, PubMed, Scifinder, Science Direct, Taylor and Francis, Wiley etc., using *G. glabra* as the searching keyword. Publications not falls in criteria and non-Scopus indexed journals were excluded from the study. All the composed information retrieved through online literature search is further classified into different sections according to the requirement and objective of the paper.

Production and Metabolism

In a one of past study highest glycyrrhizin (2.5 mg/g dry weight) content through transgenic roots culture was obtained, which was approximately, 2.6 times higher than control hairy roots culture (Lu et al., 2008). In a study, CYP88D6, a cytochrome P_{450} monooxygenase gene was identified as a glycyrrhizin-biosynthetic gene, through transcript profiling-based selection from a collection of liquorice expressed sequence tags (Seki et al., 2008). It was further confirmed through an *in vitro* study on 65-day-old cultured plants. It was found that both salicylic acid and methyl jasmonate are responsible for production of glycyrrhizin and plant growth (Shabani et al., 2009). Similarly, in another study methyl jasmonate (100 μM) was found to be responsible as most efficient elicitors for the production of glycyrrhizin (109 μg/g dry weight on day 5 of elicitation) (Wongwicha et al., 2011). It was further reveal through another study that CYP72A subfamily proteins was act as a

genetic tool for production of glycyrrhizin through genetic engineering (Seki et al., 2011). In this connection use of elicitors in the production of glycyrrhizin for enhanced production of glycyrrhizin up to 108.9 ± 1.15 μg/g was further verified through another study (Putalun et al., 2011). Production of glycyrrhizin up to 8.6-fold through the application of cellulase based elicitator by using *G. glabra* root culture was further studied (De Oliveira et al., 2014). In a very recent study on *G. glabra* an improved formation of glycyrrhizin to a quick extent over a year and without changing in plant composition was observed. Where, A4 strain of *Agrobacterium rhizogenes* help to generate hairy root cultures of *G. glabra.* The amount of glycyrrhizin has been elevated by employing various biotic as well as abiotic elicitors such as $CdCl_2$, cellulose, polyethylene glycol (PEG), and mannan-oligosaccharide. Addition of 1% concentration of PEG can cause the glycyrrhizin up to 5.4-fold hihger after 24 h of vulnerability, while 200 μg/ml cellulose has elevated the amount of glycyrrhizin up to 8.6-fold after one week of exposure, whereas 10 mg/l concentration of mannan-oligosaccharide has hastened the formation of glycyrrhizin around 7.8-fold after 10 days of stress (Srivastava et al., 2019).

Metabolism

Glycyrrhizin along and other phytoconstituents present in liquorice followed various metabolic pathways are discussed and described in Fig. 2 (Zhao et al., 2018; Abdel-Wahab et al., 2021).

Potential health benefit of *G. glabra* as anti-inflammatory, antiviral and immunomodulatory agents

Several studies claiming antiinflammatory, antiviral and immunomodulatory action of *G. glabra*, bioactive compounds and its formulation along with possible mechanism of action are included and presented in table 1, 2 and 3. Some of the highlighted studies are mentioned below as per progressive development on individual section.

Anti-inflammatory activity

An earlier study concluded that both glycyrrhetinic acid and aqueous extract of liquorice possess anti-inflammatory activity, which was comparable with diclofenac sodium. Additionally, it was further recommended that activity of anti-inflammatory formulations such as famotidine or diclofinac can be further enhanced through addition of liquorice aqueous extract (Aly et al., 2005). Subsequently, ethanol extract obtained from liquorice was exhibited to improve in the survival rate, reduced plasma levels of TNF-α and IL-6, and increased IL-10 production in LPS-treated mice (Kim et al., 2006). Further, mechanism of anti-inflammatory action of glycyrrhizin by probably due to without involving ROS and without inhibiting neutrophil functions was postulated (Racková et al., 2007). Similarly, in another study, it was found that liquorice extract was able to inhibit proinflammatory cytokine through inhibition of LPS-induced IL-1β, IL-6, IL-8 and TNF-α responses of macrophages. Additionally, liquorice extract was found to be inhibited the phosphorylation of macrophage responsible for intracellular signaling inflammatory proteins pathways including NF-κB p65 nuclear and Jun proto-oncogene-encoded activator protein (AP)−1 transcription factor (Bodet et al., 2008). In another study glycyrrhizin was failed to exhibit inhibitory effect through both COX and LOX. However, *G. glabra* (without glycyrrhizin) exhibits potent anti-inflammatory through PGE-2, TXB-2 and LTB-4 inhibition as an evidence from mammalian cell assay study. It was further postulated

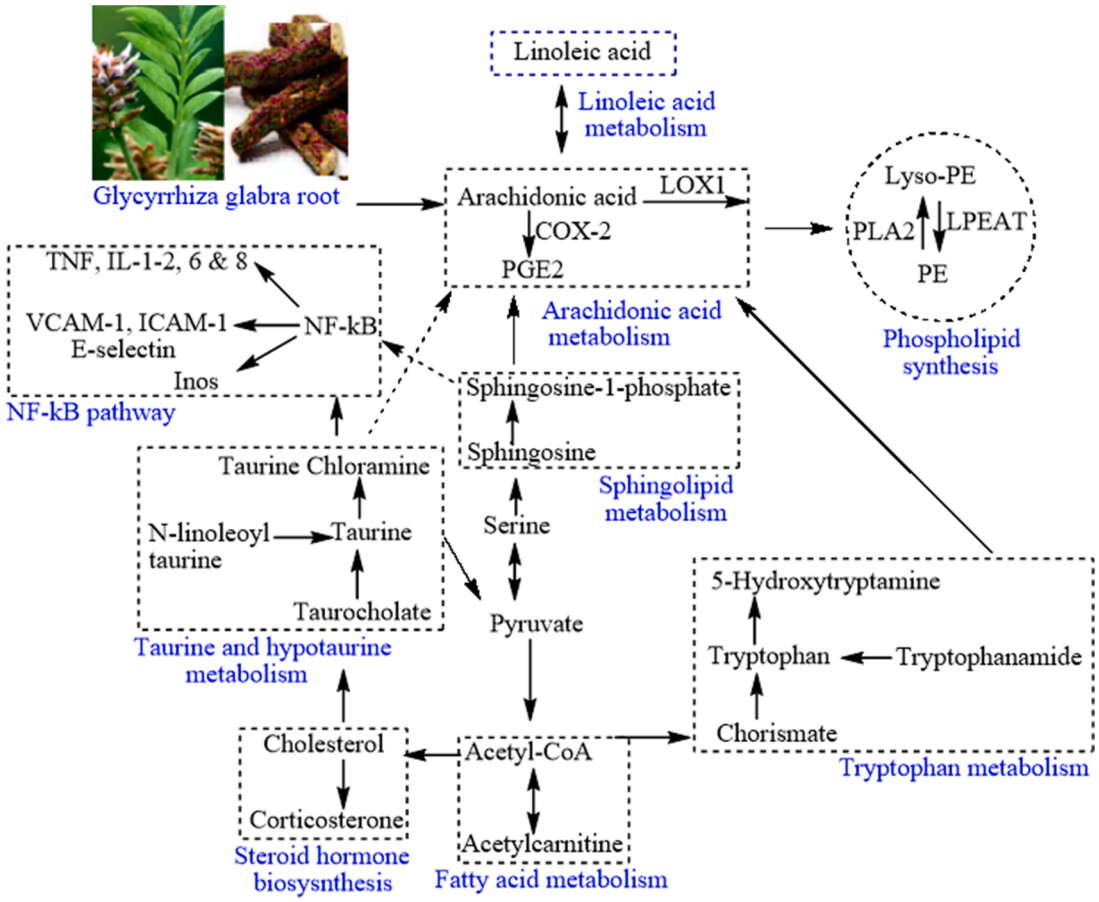

Fig. 2. Metabolic pathway of roots of *G. glabra* L.

Table 1
Anti-inflammatory, antivirals and immunomodulatory activities of *G. glabra* extracts.

Plant part/Extract/ derivatives	Pharmacological Functions	Mechanism	Doses	Reference
GutGard™ (Standardized root extract of *G. glabra*)	Anti-inflammatory action through COX and LOX inhibition- An *in vitro* studies	Inhibition of LPS induced COX-2 and LOX expression, PGE2, TXB2 and LTB4 productions.	100 and 1000 μg/ml	Chandrasekaran et al., 2011
Aqueous extract	Rheumatoid arthritis (an anti-inflammatory effect by antigen induced arthritis)	Inhibit serum levels of TNF-α and reduces antigen induce arthritis symptoms in mice.	300 mg/kg	Abd et al., 2015
Methanol extract	Anti-inflammatory effect (LPS-induced inflammation on RAW macrophages)- An *in vitro* studies	Decrease ROS and cell death by suppressing the activity of LPS induced macrophages. Downregulation of mRNA and protein expressions of iNOS, COX-2, cytokines, TNF-α, IL-1β, and IL-6 productions.	12.5–200 μg/ml	Li et al., 2015
Methanol extract and aglycone-enriched fraction	Anti-influenza Activity	Block viral replication by acting on neuraminidase enzyme.	1.70 and 0.33 μg/mL	(Grienke et al., 2014) Grienke et al., 2013
Licorice flavonoids	Pulmonary inflammation	Reduces the TNFα, IL-1β mRNA expression, elevated lung water content, and pulmonary inflammation by inhibiting the inflammatory cells infiltration and inflammatory mediator release which subsequently reduces neutrophil recruitment.	3, 10 and 30 mg/kg	(Xie et al., 2009)Xie et al., 2009

that anti-inflammatory action might be due to the presence of glabridin and isoliquiritigenin (Chandrasekaran et al., 2011). Which was further supported by another similar study establishing significant anti-inflammatory actions of extract and phytoconstituents (Nirmala and Selvaraj, 2011). During subsequent study on various extracts of liquorice, ethyl acetate extract was found to have significant anti-inflammatory effects, which was due to the presence of mainly polyphenols, flavonoids and dihydrostilbenes (Siracusa et al., 2011). In search of bioactive anti-inflammatory moiety, it was demonstrated that 5-(1,1-dimethylallyl)−3,4,4′-trihydroxy-2-methoxychalcone, licochalcone A and B, echinatin and glycycoumarin have ability to inhibit the NO, IL-6 and PGE2 productions (Fu et al., 2013). Further, dihydrostilbenes obtained from liquorice are considered to be preferred ligands for COX-2 instead of COX-1 (Trombetta et al., 2014). Progressively in another study on LPS-treated macrophages incubated with methanol extract of *G. glabra* (100 μg/mL) led to improvement of cell viability from 66.6 to 99%. Further, down regulation of NO and productions of ROS in a dose-dependent manner was established. Additionally, mRNA and protein expressions of iNOS suppression, COX-2, cytokines, TNF-α, IL-1β and IL-6 productions was observed (Li et al., 2015). Similarly, bioactive such as liquiritin, glycyrrhizic acid and liquiritigenin was found to inhibit LPS-induced pro-inflammatory mediator elevation including iNOS, COX-2, TNF-α, IL-1-β and IL-6 in BV2 cell line. However, liquorice extract was found to inhibit pro-inflammatory cytokines expression such as IL-1β, TNF-α, and IL-6) in t-BHP-treated mice liver (Yu et al., 2015). Progressively, a similar study on liquorice extract and its phytoconstituents established anti-inflammatory activity by involvement of TNF, PGE2, MMPs and free radicals cascade (Yang et al., 2017). Further, protective effect on gastric tumorigenesis by 18-β-glycyrrhetinic acid was established by anti-inflammatory action through PGE2-EP2 receptor-mediated arachidonic acid pathway (Cao et al., 2018). In another study, two isolates namely isoliquiritigenin and naringenin from liquorice was identified to improve T cells synthesis and regulation involve for anti-inflammatory action (Tiwari et al., 2018). In another study both extract and isolated compound licoflavanone was found to exhibit anti-inflammatory action on LPS-induced RAW264.7. It was further revealed that licoflavanone cause downregulation of pro-inflammatory cytokines, expression of COX-2/iNOS levels and modulation of NF-kB/MAPK pathway (Frattaruolo et al., 2019). Some liquorice flavonoid including leukotriene B4, L-acetyl carnitine, N-linoleoyl taurine, linoleic acid, tryptophanamide, and corticosterone suppress both formaldehyde-induced mice paw edema and alleviated the inflammation through involvement of multiple pathways (Yu et al., 2019). Moreover, multiple mechanism of action by which liquorice can contribute for development of anti-inflammatory responses are studied (Man et al., 2020). Further combination of *Chrysanthemum zawadskii*, peppermint and *Glycyrrhiza glabra* down-regulate inflammatory mediators rise and pro-inflammatory cytokines production induced by LPS (Cho et al., 2021). Among root and leaves, root extract was found to be more cyto-protective by significantly inhibiting the pro-inflammatory cascade (Marotti et al., 2021). In a very recent study the levels of IL-5, GTP, IL-13, GOT (on day 51), mRNA expression of eotaxin, CCL11, CCL24, COX-2, mucus secretion, eosinophil infiltration, and goblet cell hyperplasia was attenuated by the treatment of *G. glabra* was further support the same (Sun et al., 2021). In summary, Glycyrrhetinic acid and glycyrrhizin prohibit tissue inflammation by extenuating ROS formation and have the potency to inhibit IL-3, IL-5, IL-6, IL-10, IL-12, IL-13, IL-1β, TNF- α expression, COX-2 and eotaxin (Jahromi et al., 2019; Richard, 2021).

Antiviral activity

G. glabra and its bioactive components is well recognized and reviewed through several authenticated research findings for accompanying antiviral effects against several kinds of viruses such as DNA virus like Herpes Simplex Virus-1, Kaposi sarcoma-associated herpesvirus, Varicella zoster virus, Epstein Barr virus, Human Cytomegalo virus, etc. and RNA viruses such as Influenza A virus (IAV), H1N1 virus, H5N1 virus, Hepatitis C virus, Rotavirus, Newcastle disease virus, Human Immunodeficiency Virus, SARS-associated coronavirus and express its action via blocking the viral replication process (Nasiriasl and Hosseinzadeh, 2007; Baltina et al., 2009; Anagha et al., 2014; Wang et al., 2015; Fukuchi et al., 2016; (Sun et al., 2019)Huaccho-Rojas et al., 2020; Huan et al., 2020; 2021). In an earlier study GD4 (without any glycyrrhizic acid), compound obtained from liquorice was found to be effective antiviral agent against respiratory syncytial virus (RSV) with median TC_{50} (0.23 mg/ml), EC_{50} (28.73 μg/ml) and TI (8) (Wang et al., 2006). The major mechanisms for antiviral activity of various species of liquorice was described as reduced membrane transport, hepatitis B virus surface antigen sialylation, membrane fluidity reduction, may inhibit fusion cell with viral membrane of HIV-1, induction of interferon gamma in T-cells, inhibition of phosphorylating enzymes in vesicular stomatitis virus infection and overall reduction of viral latency (Fiore et al., 2008). Progressively another study investigated antiviral effect of glycyrrhizin against HCV with 50% reduction at a concentration of 14 ± 2 μg. It was postulated due to inhibition of full length viral particles and core gene expression or function in a dose dependent manner with synergistic effect with interferon (Ashfaq et al., 2011). Moreover, therapeutic glycyrrhizin concentrations (25 to 50 μg/ml) substantially found to inhibit H5N1-induced expression of the pro-inflammatory molecules CXCL10, IL-6, CCL2, and CCL5. The major mechanism behind the activity was interference with H5N1 replication and H5N1-induced

Table 2
Anti-inflammatory, antivirals and immunomodulatory activities from phytoconstituents isolated from *G. glabra*.

Compounds	Pharmacological Functions	Mechanism	Doses	Reference
Phytocomplexes of Leaves containing Licoflavanone (13)	Antioxidant and Anti-inflammatory activity (*In vitro* studies)	Inhibits LPS-induced expression of IL-1β, IL-6 and TNF-α. Decreases iNOS and COX2 expression levels. Interfere with the inflammatory cascade conciliated by NO and PGE2. Prohibits phosphorylation and activation levels of signaling molecule of the MAPK pathway (ERK1/2, JNK, and p38MAPK) and interfere with NF-kB/MAPKs pathway.	12.5–25 μg/ml	Frattaruolo et al., 2019
Phytocomplexes of Leaves (Dihydrostilbenes)	Antioxidant and anti-inflammatory activity (*In vitro* studies)	Decrease release of TxB2 and PGE2 in whole blood and inhibit only PGE2 release.	100 μg/assay	Siracusa et al., 2011
Polysaccharide fraction obtained from root and shoot	Immunomodulatory effect	Produce nitric oxide by murine peritoneal macrophage activity.	25, 50, 100 and 200 μg/ml	Nose et al., 1998
Purified fraction of water-soluble polysaccharides (10 kDa)	Immunomodulatory activity (An *in vitro* and *in vivo* studies)	Induction of IL-1, IL-6 and IL-12 productions, pinocytic activity and stimulates macrophages to produce NO.	10–400 μg/mL	Cheng et al., 2008
Polysaccharides	Immunomodulatory and anticancer activity (CT-26 colon carcinoma cell and cytokine IL-7)- *In vitro* studies	Up-regulation of the relative expression of the IL-7 gene that controls the release of immune cytokine, IL-7 and Inhibit the proliferation of tumor cell CT-26.	50 μg/ml	Ayeka et al., 2016
Polysaccharides	Immunomodulatory and anticancer activity (CT-26 tumor)- An *in vivo* studies	Suppress tumor growth, increase organ weight, organ index and activate immune cells through activation of secretion of ant-inflammatory cytokines IL-2, IL 6, and IL-7. Suppress secretion of pro-inflammatory cytokines and TNF-α. Activate $CD4^+$ and $CD8^+$ immune cells populations.	500 mg/kg	Ayeka et al., 2017
Licorice flavonoid oil	Body balance control by clinical trial	Activates AMPK in muscle cells, significantly decrease BMI and percentage of body.	300 mg capsule daily for 16 weeks	(Kinoshita et al., 2021)Kinoshita et al., 2020
Chalcones	Antiviral activity (novel influenza A (H1N1)	Inhibits neuraminidase isolated from influenza viral strain, H1N1, H9N2, novel H1N1 and oseltamivir-resistance novel H1N1 expressed in 293T cells.	0.675 to 54 μg/ml	Dao et al., 2011
Phenolics	Anti-HIV	Inhibited giant cell formation.	20 μg/ml	Hatano et al., 1988
Ammonium salt of Glycyrrhizic acid	Antiviral activity on three strains of Japanese encephalitis virus (JEV) including Nakayama, P-20,778 and 821,564 XY48.	Glycyrrhizin inhibited plaque formation in all the three strains used in the study.	500 μg/ml	(Badam, 1997) Badam, 1997
Glycyrrhizic acid (2)	Anti-viral activity (An *in vitro* studies)	Interfered with Epstein-Barr virus replication cycle.	0.04 and 4.8 mM	Lin, 2003
	Anti-asthmatic effect (An *in vivo* studies)	Suppress IL-4, IL-5 and IL-13, enhances IFN-γ, inhibit recruitment of eosinophils and mucus over production in mice with OVA-induced asthma.	10, 20, and 40 mg/kg	(Ma et al., 2013b)Ma et al., 2013b
	Immunomodulatory effect	Significantly inhibited IL-1β, IL-3, IL-5, IL-6, IL-10, IL-12 (p40), IL-12 (p70) and IL-13,	400, 80, 16 mg/L	Liu et al., 2014
	Bleomycin induced pulmonary fibrosis (An *in vivo* studies)	Ameliorated bleomycin induced pulmonary fibrosis, attenuated bleomycin induced inflammation, oxidative stress, epithelial-mesenchymal transition and activated β-signaling pathway in the lungs.	50, 100 and 200 mg/kg for 28 days	Gao et al., 2015
	Anti-inflammatory activity (An *in vitro* and *in vivo* studies)	Bio-availability improved as an evidence from improved activity.	20 and 40 mg/kg	Bernela et al., 2016
	Anti- allergic through immunomodulation (An *in vitro* studies)	Stabilized mast cells decreased vascular permeability by inhibiting the expression of Orai1, STIM1 and TRPC1, which blocked extracellular Ca^{2+} influxes.	100 mg/kg	Han et al., 2017
	Anti-inflammatory, anti-oxidation and anti-fibrotic properties in pulmonary fibrosis	It weakened expression of TGF-β1 and the phosphorylation of its downstream target, Smad2.	75 mg/kg	Zhang et al., 2017
	Anti-asthmatic (An *in vitro* and *in vivo* studies)	Inhibition of proinflammatory mediators rise like iNOS, COX-2, TNFα,Il-1β, Il-4, IL-5 and Il-6.	Various dose	Fouladi et al., 2019
Glycyrrhetic acid	Nasal inflammatory disease (An *in vivo* studies)	Inhibits HMGB1 chemotactic and mitogenic functions.	240 mg three time a week for 4 weeks	Ciprandi et al., 2020
Glycyrrhizin (3)	Anti-inflammatory on lung injury (An *in vivo* studies)	Enhanced TNF-α and IL-1β level in the pleural exudates and lung tissues of carrageenan-treated mice. Avert the neutrophils penetration into the inflamed cells by diminishing upregulation of ICAM-1, activate NF-kB and STAT-3.	10 mg/kg i.p.	Menegazzi et al., 2008
	Anti-viral	Block entry of influenza virus into cell.	1 and 0.5 mM	Wolkerstorfer et al., 2009
	Anti-asthmatic effect (An *in vivo* studies)	Reduced OVA-specific IgE levels in serum and TH2 cytokine, IL-4, and IL-5 levels in	10 mg/kg	Hocaoglu et al., 2011

(*continued on next page*)

Table 2 (*continued*)

Compounds	Pharmacological Functions	Mechanism	Doses	Reference
		bronchoalveolar lavage fluid, and maintain IgG2a levels.		
	Anti-inflammatory activity	Inhibits NF-κβ activation, MAPK signal cascade stimulated by TLR9 and TLR4 agonists and blocked induction of pro-inflammatory mediators induced by the TLR.	1 mM	Schröfelbauer et al., 2009
	Immunomodulatory effect	Up-regulated the expression of CD40, CD86 and MHC-II maturation on dendritic cells. Further, improve production of IL-12.	0.1 to 200 μg/ml	Bordbar et al., 2012
	Antiviral and immune-stimulant activity (An *in vitro* and *in vivo* studies)	Inhibits cytopathic effect of DHV (Duck Hepatitis Virus)	10 mg/kg	Soufy et al., 2012
	Acute lung injury (An *in vitro* studies)	Significantly decreased protein contents, inflammatory cells count, TNFα, IL-6, IL-α, MPO activity as well as expression of COX-2, iNOS, and NF-κB.	50 mg/kg via tail vein	Lee et al., 2019
	Anti-viral effect against SARS COV2Vero E6 and 293T cells	Cease Lenti-S infection by inhibiting the S protein-mediated cell binding.	0.5–5 mM	Li et al., 2021c
	SARS-CoV-2(*in-vitro*)	Inhibit the main protease Mpro that blocks the SARS-CoV-2 replication.	0.5–1 mg/mL	van de Sand et al., 2021
Glycyrrhetinic acid (6) and derivatives	Anti-inflammatory activity (An *in vivo* studies)	Depressed granulation tissue formation, suppressed tuberculin reaction, depress swelling.	5 mg/kg	Finney and Somers, 1958
	Antiviral activity against Zika virus (An *in vitro* studies)	Inhibits cytopathic effect (CPE), viral protein synthesis and replication stages of virus.	Different dose	Baltina et al., 2021
Glycyrrhizic acid (2) and 18β-glycyrrhetinic acid (6)	Anti-inflammatory	Suppresses the generation NO, PGE2, and ROS. Also downregulate the expression of pro-inflammatory genes through inhibition of NF-kB and PI3K activity.	10–75 μg/mL	Wang et al., 2011
Glycyrrhizic acid (2) and Glycyrrhetinic acids (6)	Immunomodulatory and Anti-inflammatory potentials	Inhibits IL-1β, IL-3, IL4, IL-5, IL-6, IL-10, IL-12, IL-13, eotaxin, and TNF-α expression.	Various dose	Richard, 2021
18 β-glycyrrhetinic acid (6)	Antitussive activity (An *in vivo* studies)	Exhibits central antitussive activity.	1 mg/kg	Anderson and Smith, 1961
18α-glycyrrhetinic acid (6)	Immunomodulatory activity	Lower CD40, MHC-II levels, decreased T-cell proliferation and IFN-γ level.	10 μg/gm	Ebrahimnezhad et al., 2016
Licochalcone	Anti-inflammatory activity (An *in vitro* and *in vivo* studies)	Down regulated TNF-α, IL-6, and IL-1-β levels.	20, 40 and 80 mg/kg	Chu et al., 2012
Licochalcone E	Anti-inflammatory activity	Decreased release of NO, PGE2, mRNA expression and secretion of IL-6, IL-1β and TNF-α.	0.5 - 2 mg	Lee et al., 2013
Licochalcone A	Anti-inflammatory activity in parkinson disease model	Inhibits production of pro-inflammatory mediators and microglial activation by blocking the phosphorylation of ERK1/2 and NF-κB, p65 in BV-2 cells. Also, attenuates decreases in dopamine uptake and tyrosine hydroxylase-immunoreactive loss.	0.625–2.5 μg/ml for 1 h	Huang et al., 2017
	Anti-inflammatory	Inhibits the *P. acnes*-induced degradation of pro-caspase-1 to caspase-1(p10) and cleavage of pro-IL-1β to IL-1β in BMDMs and also reduces the secretion of IL-1β in BMDMs.	1.25% or 2.5% in 20 μl in 3:1 mixture of acetone and olive oil through topical	Yang et al., 2018
	Cancer immunotherapy	Down-regulates the IFN-γ-induced PD-L1 protein expression and membrane localization in human lung cancer cells. Decreases the apoptosis and proliferative inhibition of Jurkat T cells caused by IFN-γ-induced PD-L1-expressing in A549 cells in the co-culture system.	10 μM	Yuan et al., 2021
Liquiritin (7)	Effective in acute lung injury (An *in vivo* studies)	Inhibited capsaicin and allyl isothiocyanate evoked TRPV1, TRPV1. Supressed inflammation and activation of NF-κβ signaling pathway in lung tissues.	25, 50 and 100 mg/kg	Liu et al., 2020
Isoliquiritigenin (32)	Smooth muscle relaxant (An *in vivo* and *in-vitro* studies)	Activated sGC, cGMP/PKG signaling cascade, inhibited PDEs and through Ca^{++} channels relaxed tracheal smooth muscles.	5, 10 and 20 mg/kg	Liu et al., 2008
	Anti-inflammatory activity (An *in vivo* and *ex-vivo* studies)	Inhibited NLRP3, activated AIM2 and ASC oligomerization.	Different dose	Honda et al., 2014
Isoliquiritigenin (32) and Naringenin	Immunomodulatory potential	Increases the numbers of Treg cells in purified naive CD4+ T cells stimulated by CD3 and CD28 antibody and TGFβ.	0.3–30 μM for isoliquiritigenin and 3–200 μM for naringenin)	Guo et al., 2015
Isoliquiritigenin (32)	Anti-inflammatory	Suppressed lipid A-induced phosphorylation of IκBα, Jnk, and p38 that decrease TNF-α and fibrosis-related gene expression.	3~10 μM	Watanabe et al., 2016
Licocoumarone	Pulmonary inflammation	Inhibit LPS-induced expression of cytokines including IL-1β, IL-6 and IL-10, without altering TNF-α at both mRNA and protein levels.	0–50 μM	Wu et al., 2017

* Chemical structure of important compound are given in Fig. 1.

Table 3
Anti-inflammatory, antivirals and immunomodulatory activities of herbal formulation containing *G. glabra*.

Herbal Formulation	Pharmacological Functions	Mechanism	Doses	Reference
Herbal mixture	Anti-asthmatic activity (Clinical trial)	Decreased the severity of cough and night time awakenings.	5 ml (Thrice daily for 5 days	Javid et al., 2019
He-Jie-Shen-Shi decoction	Effective against Corona virus disease	Regulated HIF-1, NOD-like receptor, TNF-α, T cell receptor, sphingolipid, PI3K-Akt, toll-like receptor, VEGF, Fox O and MAPK signaling pathways.	200 mg (Thrice daily)	Hu et al., 2021
Herbal Medicine Formula	Anti-asthmatic activity (An *in vivo* studies)	Identified potential biomarkers responsible for allergic asthma such as L-acetylcarnitine (L1), thromboxane B2 (L2), 10-HDoHE (L10), and 5-HETE (L11).	9.47 gm/kg (once daily for 22 days).	Yu et al., 2017
Traditional herbal formulation	Anti-inflammatory activity	Decreased production of TARC, MDC, RANTES, and IL-8. Further, down-regulated the mRNA expression of TARC, MDC, RANTES and IL-8 induced by TNF-α and IFN-γ in a dose-dependent manner.	125, 250, and 500 μg/ml	Jeong et al., 2015
Igongsan	Anti-inflammatory activity	Regulated the activation of NF-κB and caspase-1 in LPS-stimulated mouse peritoneal macrophages.	1 mg/ml	Kim et al., 2014
Herbal mixture	Anti-influenza (Clinical trial)	Decreases IFN-α level.	2.5 g (Thrice daily)	Nabeshima et al., 2012
Herbal medicine	Anti-asthma	Inhibit production of IL-4, a key Th2 cytokine involved in allergic airway inflammation in asthma.	4, 20, 100 and 500 μg/mL	Jayaprakasam et al., 2013
Herbal combinations	Chronic obstructive pulmonary disease	Inhibit neutrophilic airway inflammation by regulating the expression of inflammatory cytokines and CXCL-2 by blocking the IL-17/STAT3 pathway.	50, 100 and 200 mg/kg	Kim et al., 2020
Combination of Glycyrrhizic acid, Vitamin C and Curcumin	Effective immunomodulator anti-inflammatory agent against Coronavirus	Formulation show Immunomodulator activity against CoV infections and inhibit the inflammatory response to avert the onset of cytokine storm.	*In silico*	Chen et al., 2020b
Saiboko	Bronchial asthma	Inhibit lymphocyte proliferation and release of chemical mediators from PBMC.	100 mg/kg	Taniguchi et al., 2000

pro-inflammatory gene expression including inhibition of H5N1-induced formation of ROS and reduced activation of NFκB, JNK, and p38, redox-sensitive signaling events (Michaelis et al., 2011). In another study liquorice (including 18β-GA) was found to be effective against human RSV infection on airway epithelial cells mainly by preventing viral attachment, internalization, and by stimulating IFN secretion. (Feng-Yeh et al., 2013). A supportive study on *G. glabra* aqueous extract for novel antiviral medication was further established

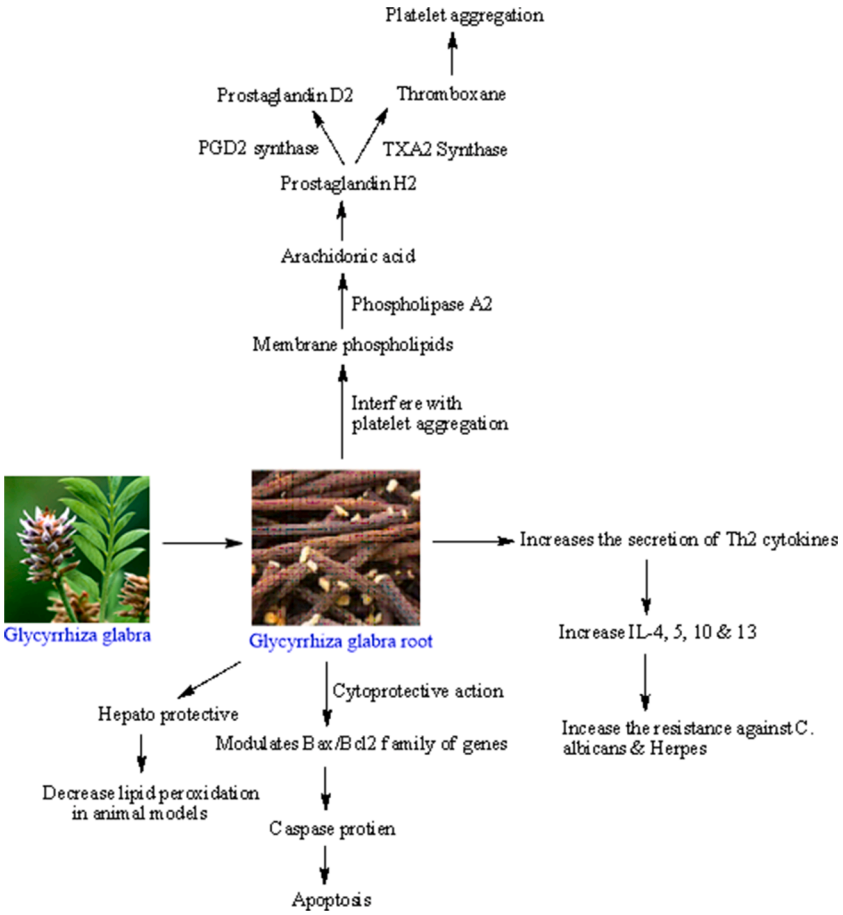

Fig. 3. Immunomodulators effects of *G. glabra* L.

(Ghannad et al., 2014). Moving ahead a study further confirmed that *G. glabra* extract (60 mg/100 ml) was nontoxic to embryonated eggs and able to inhibits replication of Newcastle disease virus (NDV) (Omer et al., 2014). Similarly, another study further revealed the antiviral activity of methanol extract of *G. glabra* (300 μg/ml) leaves against NDV through *in vivo* experimentation (Ashraf et al., 2017). Subcutaneous immunization of mice with an immunostimulating complex containing Glabilox (a saponin rich fraction of *G. glabra*) and H7N1 influenza virus antigens induce high levels of humoral and cellular response. Further, chickens vaccinated with the same immunostimulating complex protected 100% of the animals after experimental infection with a homologous virus support Glabilox as a great promising safe and effective alternative adjuvants (Alexyuk et al., 2019). Additionally, a recent study claims liquorice as a promising source of novel antiviral compounds against tobacco mosaic virus (Parizipour and Shahriari, 2020). *G. glabra* are also considered as a adaptogens in prophylaxis and treatment of several viral respiratory infections (Panossian and Brendler, 2020). In a very recent study liquorice root membrane may be considered to be used to produce a biobased face mask to control COVID-19 spread (Chowdhury et al., 2021). Further recently a study demonstrated effects of crude extracts of *G. glabra* along with other plant extract against IAV titer ($P \leq 0.05$) (Mehrbod et al., 2021). Similarly, a very recent study demonstrated noncovalent binding interaction of isoliquiritin (an isolate of *G. glabra*) with HIV-NCp7 (C-terminal zinc finger) (Wang et al., 2021).

Immunomodulatory activity

G. glabra was reviewed multiple time as a very cost effective and easily available immunomodulator (Fig. 3) as an evidence from several published studies (Kumar and Kumar, 2013; Tiwari et al., 2018). In an earlier study, highest immunological efficacy of mono extract of Glycyrrhiza and in combination with Echinacea was observed, when compared with Revitonil (Wagner and Jurcic, 2002). Similarly, in another study purified polysaccharides obtained from *G. glabra* was found to modulate macrophage immune functions (Cheng et al., 2008). Further, immunostimulant effect of aqueous extract of *G. glabra* roots was observed with increased phagocytosis through carbon clearance test, haemaggultination antibody titre value and delayed type hypersensitivity at dose levels of 150 and 300 mg/kg of body weight (Bagherwal et al., 2009). Additionally, earlier findings suggest immunostimulating activity of polysaccharides obtained from *G. glabra* through elevation of IgG, IgM, and IgA level at blood serum of mice (Hong et al., 2009). Similarly, immunostimulant activity was observed after treatment of liquorice as an evidence from higher saliva IgA production (Katayama et al., 2011). In another study glycyrrhizin cause upregulation of CD40, CD86 and MHC-II expression, mainly responsible for maturation and function of mouse splenic DCs as an evidence from higher IL-12 production (Bordbar et al., 2012). Additionally, immunomodulatory activity of aqueous extract of *G. glabra* root at the dose 1.5 g/kg/body weight was demonstrated in combination with zinc through both *in vitro* and *in vivo* experiments (Mazumder et al., 2012). Immunomodulatory properties of the hydroalcohol extract of *G. glabra* roots was further assessed on Naval Medical Research Institute (NMRI)-mice challenged with sheep red blood cells (SRBCs) suggested significant increase in the level of anti-SRBC antibody and thus improve immune system (Abtahifroushani et al., 2014). However, a research finding observed against immuno-stimulation ($P > 0.05$) by liquorice extract given with drinking water as an evidence from no any significant change on several immunological parameters tested for Influenza and Newcastle disease (Moradi et al., 2014). Progressively, another study suggested that promotion of regulatory T cell induction could be an underlying mechanism of liquorice action against autoimmune and inflammatory diseases (Guo et al., 2015). Similarly, a study on low molecular weight polysaccharides (obtained from *G. glabra*) against anticancer activity, suggested up-regulation of IL-7, which was responsible for proliferation and maturation of immune cells (Ayeka et al., 2016). Additionally, role of diet containing liquorice extract for growth and performance was further established (Elabd et al., 2016). Moreover, a study on polysaccharides (obtained from *G. glabra*) decreases TNFα and enhance the levels of IL-2, IL-6, IL-7 and serum antitumor cytokines (Ayeka et al., 2017). Further a combination containing *G. glabra* along with other plant found to exhibits immunopotentiating activity is through the modulation of biochemical factors, T-cell immunity, and transcription factors (Kaur et al., 2017). Progressively a study demonstrated usefulness of liquorice extract against pigeon paramyxovirus type 1 (PPMV-1) through series of experiments by cytometric analysis for expression of genes encoding IFN-γ and surface receptors on CD^{3+}, CD^{4+} and CD^{8+} T cells (Dziewulska et al., 2018). An *in silico* docking studies on jaranol, glycyrrhizaisoflavone and isoliquiritigenin found to be inhibit the function of cPLA2 and sPLA2 in macrophages suggesting immunomodulatory functions (Avinash et al., 2021). In summary *G. glabra induces* macrophages and stimulate the immune response as an evidence from several study. Further, N-acetyl muramoyl peptide (glycyrrhizin derivative) has found to exhibit immune-stimulating efficiencies specially on influenza virus by suppression of viral replication (Huan et al., 2021). Recently, a group of researcher showed that ethanol extract of *G. glabra* containing polysaccharides enhances the immunity through elevating the extents of serum IgG, IgM and IgA as well as by enhancing the prevalence of the lymphocytes in the spleen (Ng et al., 2021). Similarly, hydroalcohol extract of *G. glabra* and glycyrrhizic acid was found to significantly exhibits therapeutic and immunomodulatory activity as evidence from experiments on *L. major*-infected BALB/c mice (Sheikhi et al., 2021).

Implication on COVID-19 infections

G. glabra and its active components have been shown promising results to combat SARS-CoV-2 infection and can be useful in treating patients with COVID-19 as on scientific evidences collected from some of the recently published reviews (Bailly and Vergoten, 2020; Fatima et al., 2020; Huaccho-Rojas et al., 2020; Jezova et al., 2020; Murck, 2020; Srivastava et al., 2020; Adithya et al., 2021; Boozari and Hosseinzadeh, 2021; Jalali et al., 2021; Khan et al., 2021; Idrees et al., 2021; Brendler et al., 2021; Diomede et al., 2021; Liana and Phanumartwiwath, 2021; Malekmohammad et al., 2021; Merarchi et al., 2021). Several mechanisms have been identified and have been depicted in Fig. 4. Moreover, several recent study on *G. glabra* in combination with standard therapies demonstrated significantly reduction of hospitalization rate and occurrence of COVID-19 symptoms (Armanini et al., 2020; Zhong et al., 2020; Gajewski et al., 2021; Li et al., 2021a; 2021b). Recently, several targets have been identified with the possible interaction of medicinal plants included liquorice as a hopeful therapeutic option for future drug (Bandyopadhyay et al., 2021; Shakhsi-Niaei et al., 2021; Tsai et al., 2021). Glycyrrhizin was studied well in past and found to be the most active molecule for inhibition of replication of the SARS-associated virus and can be utilized for treatment of SARS -associated coronavirus (Cinatl et al., 2003). Further, glycyrrhizin was considered as antiviral therapy through the prohibition of replication, penetration, and adsorption of SARS-CoV virus (Ng et al., 2021). Similarly, in a very recent study, glycyrrhizin obtained from *G. glabra* was evaluated on patients, infected with SARS-CoV prevents the replication of the SARS-CoV virus that adversely affects the lungs and also act against influenza A virus (H5N1) (Yang et al., 2020). Moreover, glycyrrhizin was also found to influences the cellular signaling pathway, incorporating transcription factors, casein kinase II and protein kinase C (Man et al., 2020). Recently, it was further postulated that triterpenoids (glycyrrhizin and glycyrrhetinic acid) present in liquorice is able to inhibit several viruses growth including SARS-CoV-2. These compounds have ability to inhibit replication of virus, reactive oxygen species formation, β-chemokines, inflammation mediated by HMGB1/TLR4 and reduction in the binding of HMGB1 to DNA (Huan et al., 2021). Chinese traditional medicinal system (CTMS) has suggested use of glycyrrhizin

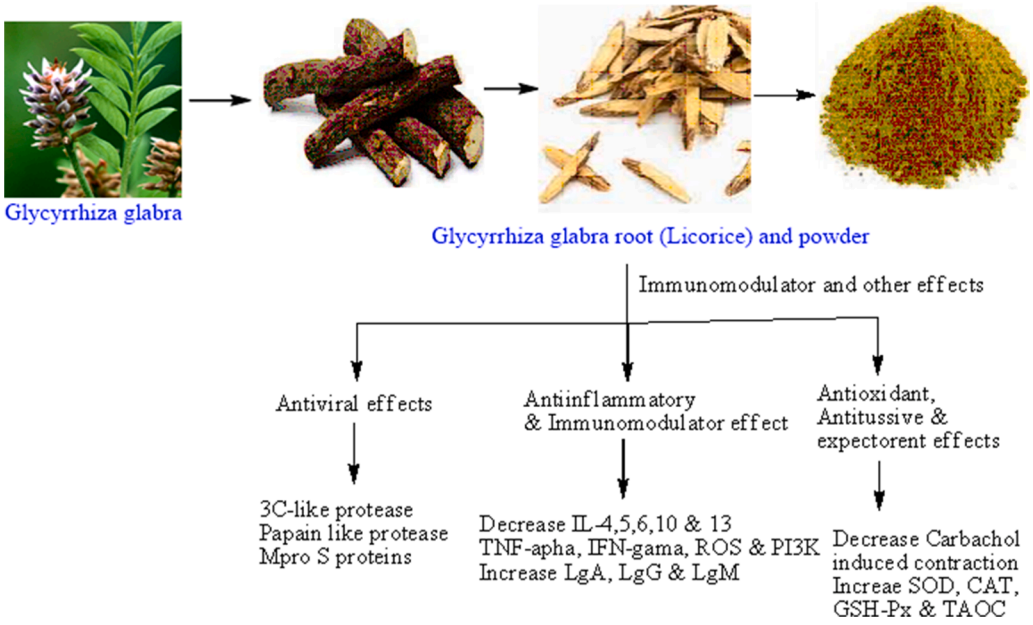

Fig. 4. Effects of *G. glabra* against COVID-19.

may be emphatic agent against the COVID-19 pandemic. Even though their unavailability of appropriate reports proves its authenticity against the COVID-19. Nevertheless the CTMS recommends other kinds of herbal remedial constituents along with glycyrrhizin. Glycyrrhizin has been prescribed by CTMS, 80 ml/day for 7 days, and 40 ml/day for 4 days for attaining antiviral properties (Jitsuiki et al., 2020). ACE-2 is considered an active receptor to which the SARS-CoV virus can adhere. It is proved from scientific reports that curtailing the extents of ACE-2 can decrease the range of entry ways for the virus to the body during the beginning of initiation of infection and further dissemination to the inner part of the body (Huan et al., 2020). Medicinal utilization of glycyrrhizin for overcoming the COVID-19 has been proceeding effective through the mechanism that involving the adherence with ACE-2. Therefore alleviating the protection of ACE-2, also obstructing the thrombin, reactive oxygen species, reducing the pro-inflammatory cytokines, and aggravating the endogenous interferons (INF) (Anand et al., 2021). Furthermore, the credibility of tissue culture infectious dose ($TCID_{50}$) assessment in characterizing the pertinent amount of aqueous extract of liquorice root (0.2 mg/mL), which have shown 50% declined cytotoxicity against Vero cell and was acceptable. The anti-herpetic action of liquorice roots has been assumed by various kinds of mechanisms viz by intervening the binding process of HSV by clear contact of extract and viruses. Moreover, the HSV-1 has been blocked by clear-cut attenuation of virus or by suppressing the binding characteristics of aqueous extract of *G. glabra*, which prohibits the binding of HSV-1 to the Vero cells by *in-vitro* medium (Ghannad et al., 2014). There is evidence related to understanding of role of liquorice in recent outbreak of COVID-19, caused by SARS-CoV-2 through *in-silico* modeling approach by targeting spike glycoprotein (PDB ID: 6VSB) and Non-structural protein-15 (NSP15) endoribonuclease (PDB ID: 6W01. As a result, it was found that the binding free energy of both glyasperin A and glycyrrhizic acid was higher towards the respective protein receptor cavity. Thus, glyasperin A and glycyrrhizic acid could be considered as the best molecule from liquorice, which could find useful against COVID-19 (Sinha et al., 2021a). This was supported by another study where leads from the liquorice plant against COVID-19 using molecular docking simulation studies investigated Mpro as a target protein having PDB ID: 6LU7. It was concluded that the compounds having oxane ring and chromenone ring substituted with hydroxyl 3-methylbut-2-enyl group could be the best alternative for the development of new leads from liquorice plant against COVID-19 (Sinha et al., 2021b).

Antiasthmatic and antitussive activity

G. glabra and its bioactive components glycyrrhizic acid have been documented and reviewed several time for prevention and treatment of respiratory tract infection including symptoms related to cough, cold and asthma (Aliavi et al., 2002; Honarmand et al., 2016; Langer et al., 2016; Chakotiya et al., 2017; Javadi et al., 2017; Fouladi et al., 2019; Ishimaru et al., 2019; Samareh Fekri et al., 2021; Wahab et al., 2021). It is evidenced that glycyrrhizin regulates the levels of T_H1/T_H2 cells and reduces the asthma in mice (Hocaoglu et al., 2011; Ma et al., 2013a; b). A polymeric formulation developed from *G. glabra* given orally in Guinea pigs at dose of 50 mg/kg/bw reduced the amount of citric acid-activated cough efforts compared to codeine (Saha et al., 2011). Granules developed from the extract of *G. glabra* in SO_2 gas-induced cough in mice have shown considerable results at 200 mg/kg/bw dose by suppressing the cough reflex compared *i.e.* around 47.13% in comparison with codeine sulfate (Shitole and Pawar, 2019). A study finds out liquiritin apioside and liquiritin as the major antitussive and expectorant compounds of liquorice through both peripheral and central mechanisms (Kuang et al., 2018).

Pharmacokinetic profile

In a very recent study on pharmacokinetic profiling of compound such as 7,4′-dihydroxyflavone, formononetin, 3-R-glabridin, isoliquiritigenin, liquiritin, naringenin 5-O-glucoside, 3,3′,4,4′-tetrahydroxy-2-methoxychalcone, liquiritinapioside, isoliquiritigenin-4′-O-β-D-apiosylglucoside and isoliquiritigenin-4-O-β-D-apiosylglucoside. It was found that out of them glabridin and 7-hydroxy-4′-methoxyisoflavone exhibits 100% of oral absorption to develop orally active direct FXa inhibitors (Ibrahim et al., 2021).

Clinical trial

Several clinical trial on *G. glabra* have been recently reported for therapeutic regimen against COVID-19 patients. In brief, single center randomized open level trial (without any placebo and blinding control) was designed on patients including both male and female to investigate

anti-inflammatory effect of *G. glabra* root extract. Trial investigated recovery rate, sign of adverse effect and time of improvement from major clinical symptoms (dry cough, fever and tiredness) and paraclinical features (lympho and thrombocytopenia) within seven days of randomization (Safa et al., 2020). A supportive clinical trial on 78-year--old man with accidental case having COVID-19 positive and acute respiratory distress symptoms speedily recovered after receiving liquorice along with intravenous immunoglobulin (Jitsuiki et al., 2020). Further, formulations containing *G. glabra* through randomized clinical trial study on 36 chronic asthma patients, with 3.5 mg/kg dose in 200 ml of water have provided favorable amelioration in pulmonary functions, as that of (0.15 mg/kg) of Prednisolone. Similarly, hydroethanol crude extract of liquorice at 100 mg/kg imparted the same results as shown by Prednisolone as an oral dose of 10 mg/kg (Silveira et al., 2020). In another trial investigating efficacy of herbal extract for improving innate immunity of COVID-19 infected patients. Evidence on the basis of declining viral load at 4th day of treatment and early recovery was assessed (Rangnekar et al., 2020).

Toxicological studies

Methanol extracts of *G. glabra* root obtained from various geographical location (total: 9 samples) were investigated for cytotoxicity study against immortal human keratinocyte (HaCaT), liver carcinoma (HepG2) and lung adenocarcinoma (A549) cell lines using the *in vitro* 3-[4,5-*dimethylthiazol*-2-*yl*]−2,5-diphenyl tetrazolium-bromide cell toxicity/viability assay. Considerable variations in cytotoxicity levels were observed among all tested samples of *G. glabra* (Basar et al., 2015). Moreover. *G. glabra* and glycyrrhizin salts are moderately toxic according to the LD_{50} have been reviewed. Single-dose at 1000 mg/kg/day not causes any death in female albino rats, but reduces attentiveness, touch sense, and locomotor function for 3 h (Nazari et al., 2017).

Conclusion and future perspectives

G. glabra is an abundantly used leguminous plant and its roots are utilized for medicinal purposes globally and also availed as a widely used sweetening agent as well as a flavoring agent by industries. It has been reported that more than 400 phytoconstituents have been merged out from the genus *Glycyrrhiza* and used therapeutically. Glycyrrhizin and glycyrrhizic acid are the leading and characteristic chemical constituents of liquorice, are liable for the sweet taste. Certainly *G. glabra* have been widely researched and found to be effective remedies as anti-inflammatory, antivirals and immunomodulation. Past and current research forced *G. glabra* and its active phytoconstituents to be effective against COVID-19 and any such future situation based on evidence. Therefore, the current study designed to deliver a content to be useful for development of future medicine and development of multiple value added product. Literature search reveal total 3908 articles including *G. glabra* as keywords are scrutinized for the requirement of current topic and out of them 198 are included in current study to finally deliver the content. Specifically, to establish liquorice and its bioactive compounds through research and review article for delivering anti-inflammatory, antivirals and immunomodulatory action is established by including several molecular mechanisms. Besides this liquorice plant has versatile therapeutic effects for the cure of many kinds of illness and also vast scope for future concerns for the treatment of various kinds of ailments including viral and immunity suppressant based infectious diseases.

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Credit authorship contribution statement

Mohmmad Rashid: Figures and Formal analysis, Rajeshwar Kamal Kant Arya and Vijay Sing Rana: Rough draft, Deepak Kumar, Sushil Kumar Chaudhary and Neeraj Kumar Sethiya: Resources, Conceptualization, Validation and Supervision. Dheeraj Bisht: Supervision, Proof reading, editing, revision and submission.

Authors agreement

Manuscript title: "**Revisiting liquorice (*Glycyrrhiza glabra*) as antivirals and immunomodulators: potential pharmacological applications with mechanistic insight**". We, the undersigning authors declare that this manuscript is original, has not been published before and is not currently being considered for publication elsewhere.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons, who satisfied the criteria for authorship, but are not listed.

We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We understand that the Corresponding Author is the sole contact for the editorial process. He is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.phyplu.2021.100206.

References

Abd, A.H., Ban, J., Qasim, B.A., Shihab, S.A., Dawood, J.O., 2015. Effect of Glycyrrhiza glabra (L.) on antigen induced arthritis in mice model. Iraqi JMS 13 (2), 129–136.

Abdel-Wahab, A.H.A., Effat, H., Mahrous, E.A., Ali, M.A., Al-Shafie, T.A., 2021. A licorice roots extract induces apoptosis and cell cycle arrest and improves metabolism via regulating MiRNAs in liver cancer cells. Nutr. Cancer 73 (6), 1047–1058. https://doi.org/10.1080/01635581.2020.1783329.

Abtahifroushani, S.M., Esmaeili Gouvarchin Ghaleh, H., Rezapor, R., Mansori Motlagh, B., Rostaei, A., 2014. Immunomodulatory effects by hydroalcoholic liquorice root extracts. J. Adv Med. Biomed. Res. 22, 112–121.

Adithya, J., Nair, B., Aishwarya, T.S., Nath, L.R., 2021. The plausible role of Indian traditional medicine in combating corona virus (SARS-CoV 2): a mini-review. Curr. Pharm. Biotechnol. 22 (7), 906–919. https://doi.org/10.2174/1389201021666200807111359.

Alagawany, M., Elnesr, S.S., Farag, M.R., 2019. Use of licorice (Glycyrrhiza glabra) herb as a feed additive in poultry: current knowledge and prospects. Animals 9, 536. https://doi.org/10.3390/ani9080536.

Alexyuk, P.G., Bogoyavlenskiy, A.P., Alexyuk, M.S., Turmagambetova, A.S., Zaitseva, I. A., Omirtaeva, E.S., Berezin, V.E., 2019. Adjuvant activity of multimolecular complexes based on Glycyrrhiza glabra saponins, lipids, and influenza virus glycoproteins. Arch. Virol. 164 (7), 1793–1803. https://doi.org/10.1007/s00705-019-04273-2.

Aliavi, A.L., Karimov, M.M., 2002. Use of glycyrrhiza extract in restoring local nonspecific defense of the lungs in patients with chronic obstructive bronchitis. Vopr. Kurortol. Fizioter. Lech. Fiz. Kult. 2, 40–41.

Aly, A.M., Al-Alousi, L., Salem, H.A., 2005. Licorice: a possible anti-inflammatory and anti-ulcer drug. AAPS Pharm. Sci. Tech. 6 (1), E74–E82. https://doi.org/10.1208/pt060113.

Anagha, K., Manasi, D., Priya, L., Meera, M., 2014. Scope of Glycyrrhiza glabra (Yashtimadhu) as an antiviral agent: a review. Int. J. Curr. Microbiol. App. Sci. 3 (12), 657–665.

Anand, A.V., Balamuralikrishnan, B., Kaviya, M., Bharathi, K., Parithathvi, A., Arun, M., Senthilkumar, N., Velayuthaprabhu, S., Saradhadevi, M., Al-Dhabi, N.A., Arasu, M. V., Yatoo, M.I., Tiwari, R., Dhama, K., 2021. Medicinal plants, phytochemicals, and herbs to combat viral pathogens including SARS-CoV-2. Molecules 26 (6), 1775. https://doi.org/10.3390/molecules26061775.

Anderson, D.M., Smith, W.G., 1961. The antitussive activity of glycyrrhetinic acid and its derivatives. J. Pharm. Pharmacol. 1961, 396–404. https://doi.org/10.1111/j.2042-7158.1961.tb11844.x.

Armanini, D., Fiore, C., Bielenberg, J., Sabbadin, C., Bordin, L., 2020. Coronavirus-19: possible therapeutic implications of spironolactone and dry extract of Glycyrrhiza glabra L. (Licorice). Front. Pharmacol. 11, 558418 https://doi.org/10.3389/fphar.2020.558418.

Ashfaq, U.A., Masoud, M.S., Nawaz, Z., Riazuddin, S., 2011. Glycyrrhizin as antiviral agent against Hepatitis C Virus. J. Transl. Med. 9, 1–7. https://doi.org/10.1186/1479-5876-9-112.

Ashraf, A., Ashraf, M.M., Rafiqe, A., Aslam, B., Galani, S., Zafar, S., Asad, F., Asghar, R. D., Akram, S., Ahmed, H., Shah, S.M.A., Asif, R., 2017. *In vivo* antiviral potential of Glycyrrhiza glabra extract against Newcastle disease virus. Pak. J. Pharm. Sci. 30 (2 (Suppl.)), 567–572.

Asl, M.N., Hosseinzadeh, H., 2008. Review of pharmacological effects of Glycyrrhiza sp. and its bioactive compounds. Phytother. Res. 22 (6), 709–724. https://doi.org/10.1002/ptr.2362.

Avinash, K.O., Sushma, P., Chandan, S., Gopenath, T.S., Kiran, M.N., Kanthesh, B.M., 2021. In silico screened flavanoids of Glycyrrhiza glabra Inhibit cPLA2 and sPLA2 in LPS stimulated macrophages. Bull. Env. Pharmacol. Life Sciences 10, 14–24.

Ayeka, P.A., Bian, Y., Mwitari, P.G., Chu, X., Zhang, Y., Uzayisenga, R., Otachi, E.O., 2016. Immunomodulatory and anticancer potential of Gan cao (Glycyrrhiza uralensis Fisch.) polysaccharides by CT-26 colon carcinoma cell growth inhibition and cytokine IL-7 upregulation *in vitro*. BMC Compl. Alternative Med. 16, 206. https://doi.org/10.1186/s12906-016-1171-4.

Ayeka, P.A., Bian, Y., Mwitari, P.G., Zhang, Y., 2017. The immunomodulatory activities of licorice polysaccharides (Glycyrrhiza uralensis Fisch.) in CT 26 tumor-bearing mice. BMC Compl. Alternative Med. 17, 536. https://doi.org/10.1186/s12906-017-2030-7.

Badam, L., 1997. *In vitro* antiviral activity of indigenous glycyrrhizin, licorice and glycyrrhizic acid (Sigma) on Japanese encephalitis virus. J. Commun. Dis. 29 (2), 91–99.

Bagherwal, P., Dahake, A.P., Chakma, C., 2009. Immunostimulant activity of aqueous extract roots of Glycyrrhiza glabra. Res. J. Pharmacol. Pharmacodyn. 1, 120–124.

Bailly, C., Vergoten, G., 2020. Glycyrrhizin: an alternative drug for the treatment of COVID-19 infection and the associated respiratory syndrome? Pharmacol. Ther. 214, 107618 https://doi.org/10.1016/j.pharmthera.2020.107618.

Baltina, L.A., Kondratenko, R.M., Plyasunova, O.A., Pokrovskii, A.G., Tolstikov, G.A., 2009. Prospects for the creation of new antiviral drugs based on glycyrrhizic acid and its derivatives (a review). Pharm. Chemistry J. 43, 539–548. https://doi.org/10.1007/s11094-010-0348-2.

Bandyopadhyay, S., Abiodun, O.A., Ogboo, B.C., Kola-Mustapha, A.T., Attah, E.I., Edemhanria, L., Kumari, A., Jaganathan, R., Adelakun, N.S., 2021. Polypharmacology of some medicinal plant metabolites against SARS-CoV-2 and host targets: molecular dynamics evaluation of NSP9 RNA binding protein. J. Biomol. Struct. Dyn. 9, 1–17. https://doi.org/10.1080/07391102.2021.1959401.

Basar, N., Oridupa, O.A., Ritchie, K.J., Nahar, L., Osman, N.M.M., Stafford, A., Kushiev, H., Kan, A., Sarker, S.D., 2015. Comparative cytotoxicity of Glycyrrhiza glabra roots from different geographical origins against immortal human keratinocyte (HaCaT), lung adenocarcinoma (A549) and liver carcinoma (HepG2) cells. Phytother. Res. 29 (6), 944–948. https://doi.org/10.1002/ptr.5329.

Batiha, G.E., Beshbishy, A.M., El-Mleeh M., A., Abdel-Daim, M.M., Devkota, H.P., 2020. Traditional uses, bioactive chemical constituents, and pharmacological and toxicological activities of Glycyrrhiza glabra L. (Fabaceae). Biomolecules 10 (3), 352. https://doi.org/10.3390/biom10030352.

Bernela, M., Ahuja, M., Thakur, R., 2016. Enhancement of anti-inflammatory activity of glycyrrhizic acid by encapsulation in chitosan-katira gum nanoparticles. Eur. J. Pharm. Biopharm. 105, 141–147. https://doi.org/10.1016/j.ejpb.2016.06.003.

Bodet, C., La, V.D., Gafner, S., Bergeron, C., Grenier, D., 2008. A licorice extract reduces lipopolysaccharide-induced proinflammatory cytokine secretion by macrophages and whole blood. J. Periodontol. 79 (9), 1752–1761. https://doi.org/10.1902/jop.2008.080052.

Boozari, M., Hosseinzadeh, H., 2021. Natural products for COVID-19 prevention and treatment regarding to previous coronavirus infections and novel studies. Phytother. Res. 35 (2), 864–876. https://doi.org/10.1002/ptr.6873.

Bordbar, N., Karimi, M.H., Amirghofran, Z., 2012. The effect of glycyrrhizin on maturation and T cell stimulating activity of dendritic cells. Cell. Immunol. 280, 44–49. https://doi.org/10.1016/j.cellimm.2012.11.013.

Bredin, C.P., 2019. Liquorice (Glycyrrhiza glabra): the journey of the sweet root from Mesopotamia to England. J. R. Coll. Physicians Edinb. 49 (2), 171–174. https://doi.org/10.4997/JRCPE.2019.222.

Brendler, T., Al-Harrasi, A., Bauer, R., Gafner, S., Hardy, M.L., Heinrich, M., Hosseinzadeh, H., Izzo, A.A., Michaelis, M., Nassiri-Asl, M., Panossian, A., Wasser, S. P., Williamson, E.M., 2021. Botanical drugs and supplements affecting the immune response in the time of COVID-19: implications for research and clinical practice. Phytother. Res. 35 (6), 3013–3031. https://doi.org/10.1002/ptr.7008.

Cao, D., Jiang, J., Zhao, D., Wu, M., 2018. The protective effects of 18-β-glycyrrhetinic acid against inflammation microenvironment in gastric tumorigenesis targeting PGE2-EP2 receptor-mediated arachidonic acid pathway. Eur. J. Inflamm. 16, 1–7. https://doi.org/10.1177/2058739218762993.

Chakotiya, A.S., Tanwar, A., Srivastava, P., Narula, A., Sharma, R.K., 2017. Effect of aquo-alchoholic extract of Glycyrrhiza glabra against Pseudomonas aeruginosa in mice lung infection model. Biomed. Pharmacother. 90, 171–178. https://doi.org/10.1016/j.biopha.2017.03.055.

Chandrasekaran, C.V., Deepak, H.B., Thiyagarajan, S., Kathiresan, P., Sangli, G.K., Deepak, M., Agarwal, A., 2011. Dual inhibitory effect of Glycyrrhiza glabra L (GutGardTM) on COX and LOX products. Phytomedicine 18, 278–284. https://doi.org/10.1016/j.phymed.2010.08.001.

Chen, K., Yang, R., Shen, F.Q., Zhu, H.L., 2020a. Advances in pharmacological activities and mechanisms of Glycyrrhizic Acid. Curr. Med. Chem. 27 (36), 6219–6243. https://doi.org/10.2174/0929867325666191011115407.

Chen, L., Hu, C., Hood, M., Zhang, X., Zhang, L., Kan, J., Du, J., 2020b. A novel combination of vitamin C, curcumin and glycyrrhizic acid potentially regulates immune and inflammatory response associated with coronavirus infections: a perspective from system biology analysis. Nutrients 12 (4), 1193. https://doi.org/10.3390/nu12041193.

Cheng, A., Wan, F., Wang, J., Jin, Z., Xu, X., 2008. Macrophage immunomodulatory activity of polysaccharides isolated from Glycyrrhiza uralensis fish. Int. Immunopharmacol. 8 (1), 43–50. https://doi.org/10.1016/j.intimp.2007.10.006.

Cho, B.O., Shin, J.Y., Kang, H.J., Park, J.H., Hao, S., Wang, F., Jang, S.I., 2021. Anti-inflammatory effect of Chrysanthemum zawadskii, peppermint, Glycyrrhiza glabra herbal mixture in lipopolysaccharide-stimulated RAW264.7 macrophages. Mol. Med. Rep. 24 (1), 532. https://doi.org/10.3892/mmr.2021.12171.

Chowdhury, M.A., Shuvho, M.B.A., Shahid, M.A., Haque, A.K.M.M., Kashem, M.A., Lam, S.S., Ong, H.C., Uddin, M.A., Mofijur, M., 2021. Prospect of biobased antiviral face mask to limit the coronavirus outbreak. Environ. Res. 192, 110294 https://doi.org/10.1016/j.envres.2020.110294.

Chu, X., Ci, X., Wei, M., Yang, X., Cao, Q., Guan, M., Li, H., Deng, Y., Feng, H., Deng, X., 2012. Licochalcone a inhibits lipopolysaccharide-induced inflammatory response *in vitro* and *in vivo*. J. Agric. Food Chem. 60 (15), 3947–3954. https://doi.org/10.1021/jf2051587.

Ciganovic, P., Jakimiuk, K., Tomczyk, M., Zovko-Koncic, M., 2019. Glycerolic licorice extracts as active cosmeceutical ingredients: extraction optimization, chemical characterization, and biological activity. Antioxidants 8 (10), 445. https://doi.org/10.3390/antiox8100445.

Cinatl, J., Morgenstern, B., Bauer, G., Chandra, P., Rabenau, H., Doerr, H.W., 2003. Glycyrrhizin, an active component of liquorice roots, and replication of SARS-associated coronavirus. Lancet 361, 2045–2046. https://doi.org/10.1016/s0140-6736(03)13615-x.

Ciprandi, G., Bellussi, L.M., Passali, G.C., Damiani, V., Passali, D., 2020. HMGB1 in nasal inflammatory diseases: a reappraisal 30 years after its discovery. Expert Rev. Clin. Immunol. 16 (5), 457–463. https://doi.org/10.1080/1744666X.2020.1752668.

Dao, T.T., Nguyen, P.H., Lee, H.S., Kim, E., Park, J., Lim, S.I., Oh, W.K., 2011. Chalcones as novel influenza A (H1N1) neuraminidase inhibitors from Glycyrrhiza inflata. Bioorg. Med. Chem. Lett. 21 (1), 294–298. https://doi.org/10.1016/j.bmcl.2010.11.016.

Dastagir, G., Rizvi, M.A., 2016. Review - Glycyrrhiza glabra L. (Liquorice). Pak. J. Pharm. Sci. 29 (5), 1727–1733.

ed. De Oliveira, C.A.F., Corassin, C.H., Corrêa, B., Oswald, I.P., 2014. Animal health: mycotoxins. In: Van Alfen, N.K. (Ed.), in Encyclopedia of Agriculture and Food Systems. Academic Press, Oxford, pp. 358–377. https://doi.org/10.1016/B978-0-444-52512-3.00200-X. ed.

Diomede, L., Beeg, M., Gamba, A., Fumagalli, O., Gobbi, M., Salmona, M., 2021. Can antiviral activity of licorice help fight COVID-19 infection? Biomolecules 11 (6), 855. https://doi.org/10.3390/biom11060855.

Dziewulska, D., Stenzel, T., Śmiałek, M., Tykałowski, B., Koncicki, A., 2018. The impact of Aloe vera and licorice extracts on selected mechanisms of humoral and cell-mediated immunity in pigeons experimentally infected with PPMV-1. BMC. Vet. Res. 14 (1), 148. https://doi.org/10.1186/s12917-018-1467-3.

Ebrahimnezhad, S., Amirghofran, Z., Karimi, M.H., 2016. Decline in immunological responses mediated by dendritic cells in mice treated with 18α-glycyrrhetinic acid. Immunol. Invest 45 (3), 191–204. https://doi.org/10.3109/08820139.2015.1113425.

Elabd, H., Wang, H.P., Shaheen, A., Yao, H., Abbass, A., 2016. Feeding Glycyrrhiza glabra (liquorice) and Astragalus membranaceus (AM) alters innate immune and physiological responses in yellow perch (Perca flavescens). Fish Shellfish Immunol 54, 374–384. https://doi.org/10.1016/j.fsi.2016.04.024.

Fatima, S., Haider, N., Alam, M.A., Gani, M.A., Ahmad, R., Taha, M., 2020. Herbal approach for the management of C0VID-19: an overview. Drug Metab. Pers. Ther. https://doi.org/10.1515/dmdi-2020-0150.

Feng Yeh, C., Wang, K.C., Chiang, L.C., Shieh, D.E., Yen, M.H., San Chang, J., 2013. Water extract of licorice had anti-viral activity against human respiratory syncytial virus in human respiratory tract cell lines. J. Ethnopharmacol 148 (2), 466–473. https://doi.org/10.1016/j.jep.2013.04.040.

Finney, R.S., Somers, G.F., 1958. The antiinflammatory activity of glycyrrhetinic acid and derivatives. J. Pharm. Pharmacol. 10 (10), 613–620. https://doi.org/10.1111/j.2042-7158.1958.tb10349.x.

Fiore, C., Eisenhut, M., Krausse, R., Ragazzi, E., Pellati, D., Armanini, D., Bielenberg, J., 2008. Antiviral effects of Glycyrrhiza species. Phytother. Res. 22 (2), 141–148. https://doi.org/10.1002/ptr.2295.

Fouladi, S., Masjedi, M., Hakemi, M.G., Eskandari, N., 2019. The review of in-vitro and in-vivo Studies over the glycyrrhizic acid as natural remedy option for treatment of allergic asthma. Iran J. Allergy Asthma Immunol. 18 (1), 1–11.

Frattaruolo, L., Carullo, G., Brindisi, B., Mazzotta, S., Bellissimo, L., Rag, V., 2019. Antioxidant and anti-inflammatory activities of flavanones from Glycyrrhiza glabra (L.) (licorice) leaf phyto-complexes: identification of licoflavanone as a modulator of

NF-kB/MAPK pathway. Antioxidants 8 (6), 186. https://doi.org/10.3390/antiox8060186.
Fu, Y., Chen, J., Li, Y.J., Zheng, Y.F., Li, P., 2013. Antioxidant and anti-inflammatory activities of six flavonoids separated from licorice. Food Chem 141 (2), 1063–1071. https://doi.org/10.1016/j.foodchem.2013.03.089.
Fukuchi, K., Okudaira, N., Adachi, K., Odai-Ide, R., Watanabe, S., Ohno, H., Yamamoto, M., Kanamoto, T., Terakubo, S., Nakashima, H., Uesawa, Y., Kagaya, H., Sakagami, H., 2016. Antiviral and antitumor activity of licorice root extracts. In Vivo (Brooklyn) 30 (6), 777–785. https://doi.org/10.21873/invivo.10994.
Gajewski, A., Kośmider, A., Nowacka, A., Puk, O., Wiciński, M., 2021. Potential of herbal products in prevention and treatment of COVID-19. Literature review. Biomed. Pharmacother. 143, 112150 https://doi.org/10.1016/j.biopha.2021.112150.
Gao, L., Tang, H., He, H., Liu, J., Mao, J., Ji, H., Lin, H., Wu, T., 2015. Glycyrrhizic acid alleviates bleomycin-induced pulmonary fibrosis in rats. Front. Pharmacol. 6, 215. https://doi.org/10.3389/fphar.2015.00215.
Ghannad, M.S., Mohammadi, A., Safiallahy, S., Faradmal, J., Azizi, M., Ahmadvand, Z., 2014. The Effect of aqueous extract of Glycyrrhiza glabra on herpes simplex virus 1. Jundishapur J. Microbiol. 7 (7), e11616. https://doi.org/10.5812/jjm.11616.
Grienke, U., Braun, H., Seidel, N., Kirchmair, J., Richter, M., Krumbholz, A., von Grafenstein, S., Liedl, K.R., Schmidtke, M., Rollinger, J.M., 2014. Computer-guided approach to access the anti-influenza activity of licorice constituents. J. Nat. Prod. 77 (3), 563–570. https://doi.org/10.1021/np400817j.
Guo, A., He, D., Xu, H., Geng, C., Zhao, J., 2015. Promotion of regulatory T cell induction by immunomodulatory herbal medicine licorice and its two constituents. Sci. Rep. 5, 14046. https://doi.org/10.1038/srep14046.
Han, S., Sun, L., He, F., Che, H., 2017. Anti-allergic activity of glycyrrhizic acid on IgE-mediated allergic reaction by regulation of allergy-related immune cells. Sci. Rep. 7 (1), 7222. https://doi.org/10.1038/s41598-017-07833-1.
Hasan, M.K., Ara, I., Mondal, M.S.A., Kabir, Y., 2021. Phytochemistry, pharmacological activity, and potential health benefits of Glycyrrhiza glabra. Heliyon 7 (6), e07240. https://doi.org/10.1016/j.heliyon.2021.e07240.
Hatano, T., Yasuhara, T., Miyamoto, K., Okuda, T., 1988. Anti-human immunodeficiency virus phenolics from licorice. Chem. Pharm. Bull (Tokyo). 36 (6), 2286–2288. https://doi.org/10.1248/cpb.36.2286.
Hocaoglu, A.B., Karaman, O., Erge, D.O., Erbil, G., Yilmaz, O., Bagriyanik, A., Uzuner, N., 2011. Glycyrrhizin and long-term histopathologic changes in a murine model of asthma. Curr. Ther. Res. Clin. Exp. 72 (6), 250–261. https://doi.org/10.1016/j.curtheres.2011.11.00.
Honarmand, A., Safavi, M., Safaei Arani, A., Shokrani, O., 2016. The efficacy of different doses of liquorice gargling for attenuating postoperative sore throat and cough after tracheal intubation. Eur. J. Anaesthesiol. 33 (8), 595–596. https://doi.org/10.1097/EJA.0000000000000400.
Honda, H., Nagai, Y., Matsunaga, T., Okamoto, N., Watanabe, Y., Tsuneyama, K., Hayashi, H., Fujii, I., Ikutani, M., Hirai, Y., Muraguchi, A., Takatsu, K., 2014. Isoliquiritigenin is a potent inhibitor of NLRP3 inflammasome activation and diet-induced adipose tissue inflammation. J. Leukoc. Biol. 96 (6), 1087–1100. https://doi.org/10.1189/jlb.3A0114-005RR.
Hong, Y.K., Wu, H.T., Ma, T., Liu, W.J., He, X.J., 2009. Effects of Glycyrrhiza glabra polysaccharides on immune and antioxidant activities in high-fat mice. Int. J. Biol. Macromol. 45 (1), 61–64. https://doi.org/10.1016/j.ijbiomac.2009.04.001.
Hosseini, M.S., Ebrahimi, M., Samsampour, D., Abadia, J., Khanahmadi, M., Amirian, R., 2020. Association analysis and molecular tagging of phytochemicals in the endangered medicinal plant licorice (Glycyrrhiza glabra L.). Phytochemistry 183, 112629. https://doi.org/10.1016/j.phytochem.2020.112629.
Hosseinzadeh, H., Nassiri-Asl, M., 2015. Pharmacological effects of Glycyrrhiza spp. and its bioactive constituents: update and review. Phytother. Res. 29, 1868–1886. https://doi.org/10.4317/medoral.19087.
Hu, H., Wang, K., Wang, L., Du, Y., Chen, J., Li, Y., Fan, C., Li, N., Sun, Y., Tu, S., Lu, X., Zhou, Z., Cui, H., 2021. He-Jie-Shen-Shi decoction as an adjuvant therapy on severe coronavirus disease 2019: a retrospective cohort and potential mechanistic study. Front. Pharmacol. 12, 700498 https://doi.org/10.3389/fphar.2021.700498.
Huaccho-Rojas, J., Balladares, A., Yanac Tellería, W., Rodríguez, C.L., Villar-López, M., 2020. Review of antiviral and immunomodulatory effects of herbal medicine with reference to pandemic COVID-19. Arch. Venez. Farmacol. Ter. 39 (6), 795–807. https://doi.org/10.5281/zenodo.4407706.
Huan, C., Chen, C., Xu, W., Guo, T., Pan, H., Gao, S., 2020. Study on antiviral activities of glycyrrhizin. Int. J. Biomed. Eng. Clin. Sci. 6 (4), 68–70. https://doi.org/10.11648/j.ijbecs.20200604.11.
Huan, C., Xu, Y., Zhang, W., Guo, T., Pan, H., Gao, S., 2021. Research progress on the antiviral activity of glycyrrhizin and its derivatives in liquorice. Front. Pharmacol. 12, 680674 https://doi.org/10.3389/fphar.2021.680674.
Huang, B., Liu, J., Ju, C., Yang, D., Chen, G., Xu, S., Zeng, Y., Yan, X., Wang, W., Liu, D., Fu, S., 2017. Licochalcone A prevents the loss of dopaminergic neurons by inhibiting microglial activation in lipopolysaccharide (LPS)-induced parkinson's disease models. Int. J. Mol. Sci. 18 (10), 2043. https://doi.org/10.3390/ijms18102043.
Ibrahim, R.S., Mahrous, R.S.R., Abu EL-Khair, R.M., Ross, S.A., Omar, A.A., Fathy, H.M., 2021. Biologically guided isolation and ADMET profile of new factor Xa inhibitors from Glycyrrhiza glabra roots using *in vitro* and in silico approaches. RSC Adv 11, 9995–10001. https://doi.org/10.1039/D1RA00359C.
Idrees, M., Khan, S., Memon, N.H., Zhang, Z., 2021. Effect of the phytochemical agents against the SARS-CoV and some of them selected for application to COVID-19: a mini-review. Curr. Pharm. Biotechnol. 22 (4), 444–450. https://doi.org/10.2174/1389201021666200703201458.
Ishimaru, N., Kinami, S., Shimokawa, T., Kanzawa, Y., Kikyo-to vs, 2019. Placebo on sore throat associated with acute upper respiratory tract infection: a randomized controlled trial. Intern. Med. 58 (17), 2459–2465. https://doi.org/10.2169/internalmedicine.2748-19.
Jahromi, B.N., Farrokhnia, F., Tanideh, N., Kumar, P.V., Parsanezhad, M.E., Alaee, S., 2019. Comparing the effects of Glycyrrhiza glabra root extract, a cyclooxygenase-2 inhibitor (celecoxib) and a gonadotropin-releasing hormone analog (diphereline) in a rat model of endometriosis. Int. J. Fertil. Steril. 13 (1), 45–50. https://doi.org/10.22074/ijfs.2019.5446.
Jalali, A., Dabaghian, F., Akbrialiabad, H., Foroughinia, F., Zarshenas, M.M., 2021. A pharmacology-based comprehensive review on medicinal plants and phytoactive constituents possibly effective in the management of COVID-19. Phytother. Res 35 (4), 1925–1938. https://doi.org/10.1002/ptr.6936.
Javadi, B., Sahebkar, A., Emami, S.A., 2017. Medicinal plants for the treatment of asthma: a traditional persian medicine perspective. Curr. Pharm. Des. 23 (11), 1623–1632. https://doi.org/10.2174/1381612822666161021143332.
Javid, A., Motevalli Haghi, N., Emami, S.A., Ansari, A., Zojaji, S.A., Khoshkhui, M., Ahanchian, H., 2019. Short-course administration of a traditional herbal mixture ameliorates asthma symptoms of the common cold in children. Avicenna J. Phytomed. 9 (2), 126–133.
Jayaprakasam, B., Yang, N., Wen, M.C., Wang, R., Goldfarb, J., Sampson, H., Li, X.M., 2013. Constituents of the anti-asthma herbal formula ASHMI (TM) synergistically inhibit IL-4 and IL-5 secretion by murine Th2 memory cells, and eotaxin by human lung fibroblasts *in vitro*. J. Integr. Med. 11 (3), 195–205. https://doi.org/10.3736/jintegrmed2013029.
Jeong, S.J., Lim, H.S., Seo, C.S., Kim, J.H., Jin, S.E., Yoo, S.R., Shin, H.K., 2015. Traditional herbal formula Jakyakgamcho-tang (Paeonia lactiflora and Glycyrrhiza uralensis) impairs inflammatory chemokine production by inhibiting activation of STAT1 and NF-kappaB in HaCaT cells. Phytomedicine 22 (2), 326–332. https://doi.org/10.1016/j.phymed.2014.12.002.
Jezova, D., Karailiev, P., Karailievova, L., Puhova, A., Murck, H., 2020. Food enrichment with Glycyrrhiza glabra extract suppresses ACE2 mRNA and protein expression in rats-possible implications for COVID-19. Nutrients 13 (7), 2321. https://doi.org/10.3390/nu13072321.
Jiang, M., Zhao, S., Yang, S., Lin, X., He, X., Wei, X., Song, Q., Li, R., Fu, C., Zhang, J., Zhang, Z., 2020. An "essential herbal medicine"-licorice: a review of phytochemicals and its effects in combination preparations. J. Ethnopharmacol. 249, 112439 https://doi.org/10.1016/j.jep.2019.112439.
Jitsuiki, K., Katayama, I., Iida, T., Yanagawa, Y., 2020. Successful treatment of elderly male with COVID-19 infection with severe acute respiratory distress syndrome using multimodal therapy, including immune modulation therapy. Cureus 12 (12), e12402. https://doi.org/10.7759/cureus.12402.
Kao, T.C., Wu, C.H., Yen, G.C., 2014. Bioactivity and potential health benefits of licorice. J. Agric. Food Chem. 62 (3), 542–553. https://doi.org/10.1021/jf404939f.
Katayama, M., Fukuda, T., Okamura, T., Suzuki, E., Tamura, K., Shimizu, Y., Suda, Y., Suzuki, K., 2011. Effect of dietary addition of seaweed and licorice on the immune performance of pigs. Anim. Sci. J. 82 (2), 274–281. https://doi.org/10.1111/j.1740-0929.2010.00826.x.
Kaur, P.Robin, Makanjuola, V.O., Arora, R., Singh, B., Arora, S., 2017. Immunopotentiating significance of conventionally used plant adaptogens as modulators in biochemical and molecular signalling pathways in cell mediated processes. Biomed. Pharmacother. 95, 1815–1829. https://doi.org/10.1016/j.biopha.2017.09.081.
Kaur, R., Kaur, H., Dhindsa, A.S., 2013. Glycyrrhiza glabra: a phytopharmacological review. Int. J. Pharm. Sci. Res. 4 (7), 2470–2477. https://doi.org/10.13040/IJPSR.0975-8232.4(7).2470-77.
Khan, T., Khan, M.A., Mashwani, Z.U., Ullah, N., Nadhman, A., 2021. Therapeutic potential of medicinal plants against COVID-19: the role of antiviral medicinal metabolites. Biocatal. Agric. Biotechnol. 31, 101890 https://doi.org/10.1016/j.bcab.2020.101890.
Kim, J.K., Oh, S.M., Kwon, H.S., Oh, Y.S., Lim, S.S., Shin, H.K., 2006. Anti-inflammatory effect of roasted licorice extracts on lipopolysaccharide-induced inflammatory responses in murine macrophages. Biochem. Biophys. Res. Commun. 345 (3), 1215–1223. https://doi.org/10.1016/j.bbrc.2006.05.035.
Kim, S.H., Hong, J.H., Yang, W.K., Geum, J.H., Kim, H.R., Choi, S.Y., Kang, Y.M., An, H. J., Lee, Y.C., 2020. Herbal combinational medication of Glycyrrhiza glabra, agastache rugosa containing Glycyrrhizic acid, tilianin inhibits neutrophilic lung inflammation by affecting CXCL2, interleukin-17/STAT3 signal pathways in a murine model of COPD. Nutrients 12 (4), 926. https://doi.org/10.3390/nu12040926.
Kim, S.J., Shin, H.J., Lee, B.J., Kim, D.S., Lee, J.H., Jeong, M.Y., Kim, H.L., Park, J., Lim, H., Kim, S.H., Hong, S.H., Hwang, M.W., Um, J.Y., 2014. The antiinflammatory mechanism of Igongsan in mouse peritoneal macrophages via suppression of NF-κB/Caspase-1 activation. Phytother. Res. 28 (5), 736–744. https://doi.org/10.1002/ptr.5058.
Kinoshita, T., Maruyama, K., Yamamoto, N., Saito, I., 2021. The effects of dietary licorice flavonoid oil supplementation on body balance control in healthy middle-aged and older Japanese women undergoing a physical exercise intervention: a randomized, double-blind, placebo-controlled trial. Aging Clin. Exp. Res. 33 (11), 3099–3108. https://doi.org/10.1007/s40520-020-01513-3.
Kuang, Y., Li, B., Fan, J., Qiao, X., Ye, M., 2018. Antitussive and expectorant activities of licorice and its major compounds. Bioorg. Med. Chem. 26 (1), 278–284. https://doi.org/10.1016/j.bmc.2017.11.046.
Kumar, K., Kumar, N.R., 2013. PA02. 14. A review on immunomodulator activity of Yashtimadhu (Glycyrrhiza glabra). Anc. Sci. Life. 32 (Suppl 2), S59. https://doi.org/10.4103/0257-7941.123878.

Kwon, Y.J., Son, D.H., Chung, T.H., Lee, Y.J., 2020. A review of the pharmacological efficacy and safety of Licorice root from corroborative clinical trial findings. J. Med. Food. 23 (1), 12–20. https://doi.org/10.1089/jmf.2019.4459.
Langer, D., Czarczynska-Goslinska, B., Goslinski, T., 2016. Glycyrrhetinic acid and its derivatives in infectious diseases. Curr. Issues Pharm. Medical Sci. 29 (3), 118–123. https://doi.org/10.1515/cipms-2016-0024.
Lee, H.N., Cho, H.J., Lim, D.Y., Kang, Y.H., Lee, K.W., Park, J.H., 2013. Mechanisms by which licochalcone exhibits potent anti-inflammatory properties: studies with phorbol ester-treated mouse skin and lipopolysaccharide-stimulated murine macrophages. Int. J. Mol. Sci. 14 (6), 10926–10943. https://doi.org/10.3390/ijms140610926.
Lee, S.A., Lee, S.H., Kim, J.Y., Lee, W.S., 2019. Effects of glycyrrhizin on lipopolysaccharide-induced acute lung injury in a mouse model. J. Thorac Dis. 11 (4), 1287–1302. https://doi.org/10.21037/jtd.2019.04.14.
Li, C., Eom, T., Jeong, Y., 2015. Glycyrrhiza glabra (L.) extract inhibits LPS-induced inflammation in RAW macrophages. J. Nutr. Sci. Vitaminol (Tokyo). 61 (5), 375–381. https://doi.org/10.3177/jnsv.61.375.
Li, J., Xu, D., Wang, L., Zhang, M., Zhang, G., Li, E., He, S., 2021c. Glycyrrhizic acid inhibits SARS-CoV-2 infection by blocking spike protein-mediated cell attachment. Molecules 26 (20), 6090. https://doi.org/10.3390/molecules26206090.
Li, X., Qiu, Q., Li, M., Lin, H., Cao, S., Wang, Q., Chen, Z., Jiang, W., Zhang, W., Huang, Y., Luo, H., Luo, L., 2021b. Chemical composition and pharmacological mechanism of ephedra-glycyrrhiza drug pair against coronavirus disease 2019 (COVID-19). Aging (Albany NY) 13 (4), 4811–4830. https://doi.org/10.18632/aging.202622.
Li, Y., Chu, F., Li, P., Johnson, N., Li, T., Wang, Y., An, R., Wu, D., Chen, J., Su, Z., Gu, X., Ding, X., 2021a. Potential effect of Maxing Shigan decoction against coronavirus disease 2019 (COVID-19) revealed by network pharmacology and experimental verification. J. Ethnopharmacol. 271, 113854 https://doi.org/10.1016/j.jep.2021.113854.
Liana, D., Phanumartwiwath, A., 2021. Leveraging knowledge of Asian herbal medicine and its active compounds as COVID-19 treatment and prevention. J. Nat. Med. 8, 1–18. https://doi.org/10.1007/s11418-021-01575-1.
Lin, J.C., 2003. Mechanism of action of glycyrrhizic acid in inhibition of Epstein-Barr virus replication *in vitro*. Antiviral Res 59 (1), 41–47. https://doi.org/10.1016/s0166-3542(03)00030-5.
Liu, B., Yang, J., Wen, Q., Li, Y., 2008. Isoliquiritigenin, a flavonoid from licorice, relaxes guinea-pig tracheal smooth muscle *in vitro* and in vivo: role of cGMP/PKG pathway. Eur. J. Pharmacol. 587 (1–3), 257–266. https://doi.org/10.1016/j.ejphar.2008.03.015.
Liu, Z., Wang, P., Lu, S., Guo, R., Gao, W., Tong, H., Yin, Y., Han, X., Liu, T., Chen, X., Zhu, M.X., Yang, Z., 2020. Liquiritin, a novel inhibitor of TRPV1 and TRPA1, protects against LPS-induced acute lung injury. Cell Calcium 88, 102198. https://doi.org/10.1016/j.ceca.2020.102198.
Liu, Z., Zhong, J.Y., Gao, E.N., Yang, H., 2014. Effects of glycyrrhizin acid and licorice flavonoids on LPS-induced cytokines expression in macrophage. Zhongguo Zhong Yao Za Zhi 39 (19), 3841–3845.
Lu, H.Y., Liu, J.M., Zhang, H.C., Yin, T., Gao, S., 2008. Ri-mediated transformation of Glycyrrhiza uralensis with a squalene synthase gene (GuSQS1) for production of glycyrrhizin. Plant Mol. Biol. Rep. 26, 1–11. https://doi.org/10.1007/s11105-008-0018-7.
Ma, C., Ma, Z., Liao, X.L., 2013a. Immunoregulatory effects of glycyrrhizic acid exerts anti-asthmatic effects via modulation of Th1/Th2 cytokines and enhancement of CD4+CD25 +Foxp3+ regulatory T cells in ovalbumin-sensitized mice. J. Ethnopharmacol. 148, 755–762. https://doi.org/10.1016/j.jep.2013.04.021.
Ma, C., Ma, Z., Liao, X.L., Liu, J., Fu, Q., Ma, S., 2013b. Immunoregulatory effects of glycyrrhizic acid exerts anti-asthmatic effects via modulation of Th1/Th2 cytokines and enhancement of CD4(+) CD25(+) Foxp3+ regulatory T cells in ovalbumin-sensitized mice. J. Ethnopharmacol. 148 (3), 755–762. https://doi.org/10.1016/j.jep.2013.04.021.
Malekmohammad, K., Rafieian-Kopaei, M., 2021. Mechanistic aspects of medicinal plants and secondary metabolites against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Curr. Pharm. Des. 27 (38), 3996–4007. https://doi.org/10.2174/1381612827666210705160130.
Mamedov, N.A., Egamberdieva, D., 2019. Phytochemical constituents and pharmacological effects of licorice: a review. Plant and Human Health (Springer, Cham) 3, 1–21. https://doi.org/10.1007/978-3-030-04408-4_1.
Man, Q., Deng, Y., Li, P., Ma, J., Yang, Z., Yang, X., Zhou, Y., Yan, X., 2020. Licorice ameliorates cisplatin-induced hepatotoxicity through antiapoptosis, antioxidative stress, anti-inflammation, and acceleration of metabolism. Front. Pharmacol. 11, 563750 https://doi.org/10.3389/fphar.2020.563750.
Marotti, I., Truzzi, F., Tibaldi, C., Negri, L., Dinelli, G., 2021. Evaluation of licorice (Glycyrrhiza glabra L.) as a novel microgreen from the anti-inflammatory potential of polyphenols. AIMS Agric. Food 6 (1), 1–13. https://doi.org/10.3934/agrfood.2021001.
Mazumder, P.M., Pattnayak, S., Parvani, H., Sasmal, D., Rathinavelusamy, P., 2012. Evaluation of immunomodulatory activity of Glycyrrhiza glabra L roots in combination with zinc. Asian Pac. J. Trop. Biomed. 2, S15–S20. https://doi.org/10.1016/S2221-1691(12)60122-1.
Mehrbod, P., Safari, H., Mollai, Z., Fotouhi, F., Mirfakhraei, Y., Entezari, H., Goodarzi, S., Tofighi, Z., 2021. Potential antiviral effects of some native Iranian medicinal plants extracts and fractions against influenza A virus. BMC Complement. Med. Ther. 21 (1), 246. https://doi.org/10.1186/s12906-021-03423-x.
Menegazzi, M., Di Paola, R., Mazzon, E., Genovese, T., Crisafulli, C., Dal Bosco, M., Zou, Z., Suzuki, H., Cuzzocrea, S., 2008. Glycyrrhizin attenuates the development of carrageenan-induced lung injury in mice. Pharmacol. Res. 58 (1), 22–31. https://doi.org/10.1016/j.phrs.2008.05.012.
Merarchi, M., Dudha, N., Das, B.C., Garg, M., 2021. Natural products and phytochemicals as potential anti-SARS-CoV-2 drugs. Phytother. Res 35 (10), 5384–5396. https://doi.org/10.1002/ptr.7151.
Michaelis, M., Geiler, J., Naczk, P., Sithisarn, P., 2011. Glycyrrhizin exerts antioxidative effects in H5N1 Influenza A virus-infected cells and inhibits virus replication and pro-inflammatory gene expression. PLoS ONE 6 (5), e19705. https://doi.org/10.1371/journal.pone.0019705.
Moradi, N., Ghazi, S., Amjadian, T., Khamisabadi, H., Habibian, M., 2014. Performance and some immunological parameter responses of broiler chickens to Licorice (Glycyrrhiza glabra) extract administration in the drinking water. Annu. Res. Rev. Biol. 4 (4), 675–683. https://doi.org/10.9734/ARRB/2014/5277.
Murck, H., 2020. Symptomatic protective action of Glycyrrhizin (Licorice) in COVID-19 infection? Front. Immunol. 11, 1239. https://doi.org/10.3389/fimmu.2020.01239.
Nabeshima, S., Kashiwagi, K., Ajisaka, K., Masui, S., Takeoka, H., Ikematsu, H., Kashiwagi, S., 2012. A randomized, controlled trial comparing traditional herbal medicine and neuraminidase inhibitors in the treatment of seasonal influenza. J. Infect. Chemother. 18 (4), 534–543. https://doi.org/10.1007/s10156-012-0378-7.
Nasiri, L., Gavahian, M., Majzoobi, M., Farahnaky, A., 2020. Rheological behavior of Glycyrrhiza glabra (Licorice) extract as a function of concentration and temperature: a critical reappraisal. Foods 9, 1872. https://doi.org/10.3390/foods9121872.
Nasiriasl, M., Hosseinzadeh, H., 2007. Review of antiviral effects of Glycyrrhiza glabra L. and its active component, glycyrrhizin. J. Med. Plants 6 (22), 1–12.
Nazari, S., Rameshrad, M., Hosseinzadeh, H., 2017. Toxicological effects of Glycyrrhiza glabra L. (Licorice): a review. Phytother. Res. 31 (11), 1635–1650. https://doi.org/10.1002/ptr.5893.
Ng, S.L., Khaw, K.Y., Ong, Y.S., Goh, H.P., Kifli, N., Teh, S.P., Ming, L.C., Kotra, V., Goh, B.H., 2021. Licorice: a potential herb in overcoming SARS-CoV-2 infections. J. Evid. Based Integr. Med. doi: 10.1177/2515690X21996662.
Nirmala, P., Selvaraj, T., 2011. Anti-inflammatory and anti-bacterial activities of Glycyrrhiza glabra (L.). J. Agric. Technol. 7 (3), 815–823.
Nose, M., Terawaki, K., Oguri, K., Ogihara, Y., Yoshimatsu, K., Shimomura, K., 1998. Activation of macrophages by crude polysaccharide fractions obtained from shoots of Glycyrrhiza glabra and hairy roots of Glycyrrhiza uralensis *in vitro*. Biol. Pharm. Bull. 21 (10), 1110–1112. https://doi.org/10.1248/bpb.21.1110.
Olukoga, A., Donaldson, D., 2000. Liquorice and its health implications. J. R. Soc. Promot. Health. 120 (2), 83–89. https://doi.org/10.1177/146642400012000203.
Omer, M.O., Almalki, W.H., Shahid, I., Khuram, S., Altaf, I., Imran, S., 2014. Comparative study to evaluate the anti-viral efficacy of Glycyrrhiza glabra extract and ribavirin against the Newcastle disease virus. Pharmacognosy Res 6 (1), 6–11. https://doi.org/10.4103/0974-8490.122911.
Pandey, S., Verma, B., Arya, P., 2017. A review on constituents, pharmacological activities and medicinal uses of Glycyrrhiza glabra. Univers. J. Pharm. Res. 2 (2), 26–31. https://doi.org/10.22270/ujpr.v2i2.RW2.
Panossian, A., Brendler, T., 2020. The Role of adaptogens in prophylaxis and treatment of Viral Respiratory Infections. Pharmaceuticals (Basel) 13 (9), 236. https://doi.org/10.3390/ph13090236.
Parizipour, M.G., Shahriari, A.G., 2020. Investigation of antiviral potential of licorice (Glycyrrhiza glabra L.) crude extract against tobacco mosaic virus. J. Anim. Plant Sci 30 (1), 107–114.
Pastorino, G., Cornara, L., Soares, S., Rodrigues, F., 2018. Liquorice (Glycyrrhiza glabra): a phytochemical and pharmacological review. Phytother. Res. 32 (12), 2323–2339. https://doi.org/10.1002/ptr.6178.
Putalun, W., Wongwicha, W., Tanaka, H., Shoyama, Y., 2011. Enhanced glycyrrhizin production in Glycyrrhiza inflata hairy roots cultures using elicitation. Planta Med. 77, PB14. https://doi.org/10.1055/s-0031-1282268.
Racková, L., Jancinová, V., Petríková, M., Drábiková, K., Nosál, R., Stefek, M., Kostálová, D., Prónayová, N., Kovácová, M., 2007. Mechanism of anti-inflammatory action of liquorice extract and glycyrrhizin. Nat. Prod. Res. 21 (14), 1234–1241. https://doi.org/10.1080/14786410701371280.
Rangnekar, H., Patankar, S., Suryawanshi, K., Soni, P., 2020. Safety and efficacy of herbal extracts to restore respiratory health and improve innate immunity in COVID-19 positive patients with mild to moderate severity: a structured summary of a study protocol for a randomized controlled trial. Trials 21 (1), 943. https://doi.org/10.1186/s13063-020-04906-x.
Rani, K., Devi, N., Saharan, V., Kharb, P., 2021. Glycyrrhiza glabra: an insight to nanomedicine. J. Nanosci. Nanotechnol. 21 (6), 3367–3378. https://doi.org/10.1166/jnn.2021.19007.
Rehman, M.U., Farooq, A., Ali, R., Bashir, S., Bashir, N., Majeed, S., Taifa, S., Ahmad, S. B., Arafah, A., Sameer, A.S., Khan, R., Qamar, W., Rasool, S., Ahmad, A., 2020. Preclinical evidence for the pharmacological actions of glycyrrhizic acid: a comprehensive review. Curr. Drug Metab. 21 (6), 436–465. https://doi.org/10.2174/1389200221666200620204914.
Ren, J., Wang, Z.G., 1988. Pharmacological research on the effect of licorice. J. Tradit. Chin. Med. 8 (4), 307–309.
Revers, R.E., 1956. Clinical and pharmacological investigations on extract of licorice. Acta Med. Scand. Suppl. 312, 749–751. https://doi.org/10.1111/j.0954-6820.1956.tb17084.x.
Richard, S.A., 2021. Exploring the pivotal immunomodulatory and anti-inflammatory potentials of glycyrrhizic and glycyrrhetinic Acids. Mediators Inflamm. 6699560, 1–15. https://doi.org/10.1155/2021/6699560.
Safa, O., Hassani-Azad, M., Farashahinejad, M., Davoodian, P., Dadvand, H., Hassanipour, S., Fathalipour, M., 2020. Effects of Licorice on clinical symptoms and laboratory signs in moderately ill patients with pneumonia from COVID-19: a

structured summary of a study protocol for a randomized controlled trial. Trials 21 (1), 790. https://doi.org/10.1186/s13063-020-04706-3.
Saha, S., Nosalova, G., Ghosh, D., Fleskova, D., Capek, P., Ray, B., 2011. Structural features and *in vivo* antitussive activity of the water extracted polymer from Glycyrrhiza glabra. Int. J. Biol. Macromol. 48 (4), 634–638. https://doi.org/10.1016/j.ijbiomac.2011.02.003.
Samareh Fekri, M., Poursalehi, H.R., Sharififar, F., Mandegary, A., Rostamzadeh, F., Mahmoodi, R., 2021. The effects of methanolic extract of Glycyrrhiza glabra on the prevention and treatment of bleomycin-induced pulmonary fibrosis in rat: experimental study. Drug Chem. Toxicol. 44 (4), 365–371. https://doi.org/10.1080/01480545.2019.1606232.
Saxena, S., 2005. Glycyrrhiza glabra: medicine Over Millennium. Nat. Prod. Radiance 4 (5), 358–367.
Schröfelbauer, B., Raffetseder, J., Hauner, M., Wolkerstorfer, A., Ernst, W., Szolar, O.H., 2009. Glycyrrhizin, the main active compound in liquorice, attenuates pro-inflammatory responses by interfering with membrane-dependent receptor signalling. Biochem. J. 421 (3), 473–482. https://doi.org/10.1042/BJ20082416.
Seki, H., Ohyama, K., Sawai, S., Mizutani, M., Ohnishi, T., Sudo, H., Akashi, T., Aoki, T., Saito, K., Muranaka, T., 2008. Licorice beta-amyrin 11-oxidase, a cytochrome P450 with a key role in the biosynthesis of the triterpene sweetener glycyrrhizin. Proc. Natl. Acad. Sci. USA. 105 (37), 14204–14209. https://doi.org/10.1073/pnas.0803876105.
Seki, H., Sawai, S., Ohyama, K., Mizutani, M., Ohnishi, T., Sudo, H., Fukushima, E.O., Akashi, T., Aoki, T., Saito, K., Muranaka, T., 2011. Triterpene functional genomics in licorice for identification of CYP72A154 involved in the biosynthesis of glycyrrhizin. Plant Cell 23 (11), 4112–4123. https://doi.org/10.1105/tpc.110.082685.
Shabani, L., Ehsanpour, A.A., Asghari, G., Emami, J., 2009. Glycyrrhizin production by *in vitro* cultured Glycyrrhiza glabra elicited by methyl Jasmonate and salicylic acid. Russ. J. Plant Physiol. 56, 621–626. https://doi.org/10.1134/S1021443709050069.
Shakhsi-Niaei, M., Soureshjani, E.H., Babaheydari, A.K., 2021. In silico comparison of separate or combinatorial effects of potential inhibitors of the SARS-CoV-2 binding site of ACE2. Iran J. Public Health. 50 (5), 1028–1036. https://doi.org/10.18502/ijph.v50i5.6120.
Sharifi-Rad, J., Quispe, C., Herrera-Bravo, J., Belén, L.H., Kaur, R., et al., 2021. Glycyrrhiza genus: enlightening phytochemical components for pharmacological and health-promoting abilities. Oxid. Med. Cell. Longev. 7571132, 1–20. https://doi.org/10.1155/2021/7571132.
Edited by Sharma, V., Katiyar, A., Agrawal, R.C., 2018. Glycyrrhiza glabra: chemistry and pharmacological activity. Sweeteners. In: Mérillon, J, Ramawat, K.G. (Eds.), Reference Series in Phytochemistry. Springer, Cham, pp. 87–100, 110.1007/978-3-319-27027-2_21.
Sheikhi, S., Khamesipour, A., Radjabian, T., Ghazanfari, T., Mohammadi, A.M., 2021. Immunotherapeutic Effects of Glycyrrhiza glabra and Glycyrrhizic Acid on Leishmania major Infected BALB/C Mice. Parasite Immunol 24, e12879. https://doi.org/10.1111/pim.12879.
Shitole, M., Pawar, V.T., 2019. Study of potential antitussive activity of Glycyrrhiza glabra granules by using a cough model induced by Sulphur dioxide gas in mice. Asian J. Pharm. Clin. Res. 12 (10), 262–267. https://doi.org/10.22159/ajpcr.2019.v12i10.339.
Silveira, D., Prieto-Garcia, J.M., Boylan, F., Estrada, O., Fonseca-Bazzo, Y.M., Jamal, C. M., Magalhães, P.O., Pereira, E.O., Tomczyk, M., Heinrich, M., 2020. COVID-19: is there evidence for the use of herbal medicines as adjuvant symptomatic therapy? Front. Pharmacol 11, 581840. https://doi.org/10.3389/fphar.2020.581840.
Sinha, S.K., Prasad, S.K., Islam, M.A., Chaudhary, S.K., Singh, S., Shakya, A., 2021b. Potential leads from liquorice against SARS-CoV-2 main protease using molecular docking simulation studies. Comb. Chem. High Throughput Screen 24 (4), 591–597. https://doi.org/10.2174/1386207323999200817103148.
Sinha, S.K., Prasad, S.K., Islam, M.A., Gurav, S.S., Patil, B.B., AlFaris, N.A., Aldayel, T.S., AlKehayez, N.M., Wabaidur, S.M., Shakyai, A., 2021a. Identification of bioactive compounds from Glycyrrhiza glabra as possible inhibitor of SARS-CoV-2 spike glycoprotein and non-structural protein-15: a pharmacoinformatics study. J. Biomol. Struct. Dyn. 39 (13), 4686–4700. https://doi.org/10.1080/07391102.2020.1779132.
Siracusa, L., Antonella Saija, A., Cristani, M., Cimino, F., D'Arrigo, M., Trombetta, D., Rao, F., Ruberto, G., 2011. Phyto-complexes from liquorice (Glycyrrhiza glabra L.) leaves - chemical characterization and evaluation of their antioxidant, anti-genotoxic, and anti-inflammatory activity. Fitoterapia 82 (4), 546–556. https://doi.org/10.1016/j.fitote.2011.01.009.
Soufy, H., Yassein, S., Ahmed, A.R., Khodier, M.H., Kutkat, M.A., Nasr, S.M., Okda, F.A., 2012. Antiviral and immune stimulant activities of glycyrrhizin against duck hepatitis virus. Afr. J. Tradit. Complement. Altern. Med. 9 (3), 389–395. https://doi.org/10.4314/ajtcam.v9i3.14.
Srivastava, M., Singh, G., Sharma, Shukla, S., Mishra, P., 2019. Elicitation enhanced the yield of glycyrrhizin and antioxidant activities in hairy root cultures of Glycyrrhiza glabra L. J. Plant Growth Regul. 38, 373–384. https://doi.org/10.1007/s00344-018-9847-2.
Srivastava, V., Yadav, A., Sarkar, P., 2020. Molecular docking and ADMET study of bioactive compounds of Glycyrrhiza glabra against main protease of SARS-CoV2. Mater. Today Proc 14. https://doi.org/10.1016/j.matpr.2020.10.055.
Sun, X., Mehrabi Nasab, E., Athari, S.M., Athari, S.S., 2021. Anti-inflammatory effect of herbal traditional medicine extract on molecular regulation in allergic asthma. Allergol. Select 5, 148–156. https://doi.org/10.5414/ALS400545.
Sun, Z., Zhao, T., Lu, N., Yang, Y., Zhu, H., 2019. Research progress of glycyrrhizic acid on antiviral activity. Mini. Rev. Med. Chem. 19, 826–832. https://doi.org/10.2174/1389557519666190119111125.
Taniguchi, C., Homma, M., Takano, O., Hirano, T., Oka, K., Aoyagi, Y., Niitsuma, T., Hayashi, T., 2000. Pharmacological effects of urinary products obtained after treatment with Saiboku-to, a herbal medicine for bronchial asthma, on type IV allergic reaction. Planta Med. 66 (7), 607–611. https://doi.org/10.1055/s-2000-8626.
Tiwari, R., Latheef, S.K., Ahmed, I., Iqbal, H.M.N., 2018. Herbal immunomodulators - a remedial panacea for designing and developing effective drugs and medicines: current scenario and future prospects. Curr. Drug Metab. 19 (3), 264–301. https://doi.org/10.2174/1389200219666180129125436.
Trombetta, D., Giofrè, S.V., Tomaino, A., Raciti, R., Saija, A., Cristani, M., Romeo, R., Siracusa, L., Ruberto, G., 2014. Selective COX-2 inhibitory properties of dihydrostilbenes from liquorice leaves–in vitro assays and structure/activity relationship study. Nat. Prod. Commun. 9 (12), 1761–1764.
Tsai, M.S., Yang, Y.H., Lin, Y.S., Chang, G.H., Hsu, C.M., Yeh, R.A., Shu, L.H., Cheng, Y. C., Liu, H.T., Wu, Y.H., Wu, Y.H., Shen, R.C., Wu, C.Y., 2021. GB-2 blocking the interaction between ACE2 and wild type and mutation of spike protein of SARS-CoV-2. Biomed. Pharmacother. 142, 112011 https://doi.org/10.1016/j.biopha.2021.112011.
van de Sand, L., Bormann, M., Alt, M., Schipper, L., Heilingloh, C.S., Steinmann, E., Todt, D., Dittmer, U., Elsner, C., Witzke, O., 2021. Glycyrrhizin effectively inhibits SARS-CoV-2 replication by inhibiting the viral main protease. Viruses 13, 609. https://doi.org/10.3390/v13040609.
Wagner, H., Jurcic, K., 2002. Immunological studies of Revitonil, a phytopharmaceutical containing Echinacea purpurea and Glycyrrhiza glabra root extract. Phytomedicine 9 (5), 390–397. https://doi.org/10.1078/09447110260571616.
Wahab, S., Ahmad, I., Irfan, S., Siddiqua, A., Usmani, S., Ahmad, M.P., 2021. Pharmacological Efficacy and Safety of Glycyrrhiza glabra in the treatment of respiratory tract infections. Mini Rev. Med. Chem. https://doi.org/10.2174/1389557521666210927153001.
Wang, C., Chen, L., Xu, C., Shi, J., Chen, S., Tan, M., Chen, J., Zou, L., Chen, C., Liu, Z., Liu, X., 2020. A comprehensive review for phytochemical, pharmacological, and biosynthesis studies on Glycyrrhiza spp. Am. J. Chin. Med. 48 (1), 17–45. https://doi.org/10.1142/S0192415X20500020.
Wang, C.Y., Kao, T.C., Lo, W.H., Yen, G.C., 2011. Glycyrrhizic acid and 18β-glycyrrhetinic acid modulate lipopolysaccharide-induced inflammatory response by suppression of NF-κB through PI3K p110δ and p110γ inhibitions. J. Agric. Food Chem. 59 (14), 7726–7733. https://doi.org/10.1021/jf2013265.
Wang, L., Yang, R., Yuan, B., Liu, Y., Liu, C., 2015. The antiviral and antimicrobial activities of licorice, a widely-used Chinese herb. Acta Pharm. Sin. B 5, 310–315. https://doi.org/10.1016/j.apsb.2015.05.005.
Wang, R., Wei, Y., Wang, M., Yan, P., Jiang, H., Du, Z., 2021. Interaction of natural compounds in licorice and turmeric with HIV-NCp7 zinc finger domain: potential relevance to the mechanism of antiviral activity. Molecules 26 (12), 3563. https://doi.org/10.3390/molecules26123563.
Wang, X.Q., Li, H.Y., Liu, X.Y., Zhang, F.M., Li, X., Piao, Y.A., Xie, Z.P., Chen, Z.H., Li, X., 2006. The anti-respiratory syncytial virus effect of active compound of Glycyrrhiza GD4 *in vitro*. Zhong Yao Cai 29 (7), 692–694.
Watanabe, Y., Nagai, Y., Honda, H., Okamoto, N., Yamamoto, S., Hamashima, T., Ishii, Y., Tanaka, M., Suganami, T., Sasahara, M., Miyake, K., Takatsu, K., 2016. Isoliquiritigenin attenuates adipose tissue inflammation *in vitro* and adipose tissue fibrosis through inhibition of innate immune responses in mice. Sci. Rep. 6, 23097. https://doi.org/10.1038/srep23097.
Wolkerstorfer, A., Kurz, H., Bachhofner, N., Szolar, O.H., 2009. Glycyrrhizin inhibits influenza A virus uptake into the cell. Antiviral. Res. 83 (2), 171–178. https://doi.org/10.1016/j.antiviral.2009.04.012.
Wongwicha, W., Tanaka, H., Shoyama, Y., Putalun, W., 2011. Methyl jasmonate elicitation enhances glycyrrhizin production in Glycyrrhiza inflata hairy roots cultures. Z. Naturforsch. C. J. Biosci. 66 (7–8), 423–428. https://doi.org/10.1515/znc-2011-7-815.
Wu, L., Fan, Y., Fan, C., Yu, Y., Sun, L., Jin, Y., Zhang, Y., Ye, R.D., 2017. Licocoumarone isolated from Glycyrrhiza uralensis selectively alters LPS-induced inflammatory responses in RAW 264.7 macrophages. Eur. J. Pharmacol. 801, 46–53. https://doi.org/10.1016/j.ejphar.2017.02.049.
Xie, Y.C., Dong, X.W., Wu, X.M., Yan, X.F., Xie, Q.M., 2009. Inhibitory effects of flavonoids extracted from licorice on lipopolysaccharide-induced acute pulmonary inflammation in mice. Int. Immunopharmacol. 9 (2), 194–200. https://doi.org/10.1016/j.intimp.2008.11.004.
Yang, F., Zhang, Y., Tariq, A., Jiang, X., Ahmed, Z., Zhihao, Z., Idrees, M., Azizullah, A., Adnan, M., Bussmann, R.W., 2020. Food as medicine: a possible preventive measure against coronavirus disease (COVID-19). Phytother. Res. 24 (12), 3124–3136. https://doi.org/10.1002/ptr.6770.
Yang, G., Lee, H.E., Yeon, S.H., Kang, H.C., Cho, Y.Y., Lee, H.S., Zouboulis, C.C., Han, S. H., Lee, J.H., Lee, J.Y., 2018. Licochalcone A attenuates acne symptoms mediated by suppression of NLRP3 inflammasome. Phytother. Res. 32 (12), 2551–2559. https://doi.org/10.1002/ptr.6195, 2018 Dec.
Yang, R., Wang, L.Q., Yuan, B.C., Liu, Y., 2015. The pharmacological activities of Licorice. Planta Med 81 (18), 1654–1669. https://doi.org/10.1055/s-0035-1557893.
Yang, R., Yuan, B.C., Ma, Y.S., Zhou, S., Liu, Y., 2017. The anti-inflammatory activity of licorice, a widely used Chinese herb. Pharm. Biol. 55 (1), 5–18. https://doi.org/10.1080/13880209.2016.1225775.
Yu, J., Ha, J.Y., Kim, K., Jung, Y., 2015. Anti-inflammatory activities of licorice extract and its active compounds, glycyrrhizic acid, liquiritin, and liquiritigenin, in BV2 cells and mice liver. Molecules 20 (7), 13041–13054. https://doi.org/10.3390/molecules200713041.

Yu, M., Jia, H.M., Cui, F.X., Yang, Y., Zhao, Y., Yang, M.H., Zou, Z.M., 2017. The Effect of Chinese herbal medicine formula mKG on allergic asthma by regulating lung and pasma metabolic alternations. Int. J. Mol. Sci. 18 (3), 602. https://doi.org/10.3390/ijms18030602.

Yu, X., Bao, Y., Meng, X., Wang, S., Li, T., Chang, X., Xu, W., Yang, G., Bo, T., 2019. Multi-pathway integrated adjustment mechanism of licorice flavonoids presenting anti-inflammatory activity. Oncol. Lett. 18 (5), 4956–4963. https://doi.org/10.3892/ol.2019.10793.

Yuan, L.W., Jiang, X.M., Xu, Y.L., Huang, M.Y., Chen, Y.C., Yu, W.B., Su, M.X., Ye, Z.H., Chen, X., Wang, Y., Lu, J.J., 2021. Licochalcone A inhibits interferon-gamma-induced programmed death-ligand 1 in lung cancer cells. Phytomedicine 80, 153394. https://doi.org/10.1016/j.phymed.2020.153394.

Zhang, D., Liu, B., Cao, B., Wei, F., Yu, X., Li, G.F., Chen, H., Wei, L.Q., Wang, P.L., 2017. Synergistic protection of Schizandrin B and Glycyrrhizic acid against bleomycin-induced pulmonary fibrosis by inhibiting TGF-β1/Smad2 pathways and overexpression of NOX4. Int. Immunopharmacol. 48, 67–75. https://doi.org/10.1016/j.intimp.2017.04.024.

Zhao, F., Gao, L., Qin, X., Du, G., Zhou, Y., 2018. The intervention effect of licorice in D-galactose induced aging rats by regulating the taurine metabolic pathway. Food Funct 9, 4814–4821. https://doi.org/10.1039/c8fo00740c.

Zhong, L.L.D., Lam, W.C., Yang, W., Chan, K.W., Sze, S.C.W., Miao, J., Yung, K.K.L., Bian, Z., Wong, V.T., 2020. Potential targets for treatment of coronavirus disease2019 (COVID-19): a review of Qing-Fei-Pai-Du-Tang and its major herbs. Am. J. Chin. Med. 48 (5), 1051–1071. https://doi.org/10.1142/S0192415X20500512.